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<p>(51) International Patent Classification <sup>7</sup> : <b>C07K 14/00</b></p>	<p><b>A2</b></p>	<p>(11) International Publication Number: <b>WO 00/26245</b></p> <p>(43) International Publication Date: <b>11 May 2000 (11.05.00)</b></p>																																				
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<p>(57) Abstract</p> <p>The invention provides human membrane transport proteins (MTRP) and polynucleotides which identify and encode MTRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MTRP.</p>																																						

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## MEMBRANE TRANSPORT PROTEINS

## TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of membrane transport  
5 proteins and to the use of these sequences in the diagnosis, treatment, and prevention of membrane  
transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

## BACKGROUND OF THE INVENTION

Eukaryotic cells are bound by a lipid bilayer membrane and subdivided into functionally  
10 distinct, membrane bound compartments. The membranes maintain essential differences between the  
cytosol, the extracellular environment, and the contents of intracellular organelles such as the Golgi or  
the endoplasmic reticulum. As lipid membranes are highly impermeable to most polar molecules,  
transport of essential nutrients; metal ions such as  $K^+$ ,  $NH_4^+$ ,  $P_i$ ,  $SO_4^{2-}$ ; sugars; vitamins; metabolic  
waste products; cell signaling molecules; drugs; peptides; and proteins and other macromolecules  
15 across lipid membranes and between organelles must be mediated by a variety of transport molecules.  
Many transport mechanisms are substrate specific, with each transport protein carrying particular  
members of a molecular class, such as ions, sugars, or amino acids, across membranes. For example,  
amino acids are imported into cells via specific amino acid permeases.

Transport proteins are multi-pass transmembrane proteins, which either actively transport  
20 molecules across the membrane or passively allow them to cross. Active transport involves  
directional pumping of a solute across the membrane, usually against an electrochemical gradient.  
Active transport is tightly coupled to a source of metabolic energy, such as ATP hydrolysis or an  
electrochemically favorable ion gradient. Passive transport involves the movement of a solute down  
its electrochemical gradient. Transport proteins can be further classified as either carrier proteins or  
25 channel proteins. Carrier proteins, which can function in active or passive transport, bind to a specific  
solute to be transported and undergo a conformational change which transfers the bound solute across  
the membrane. Channel proteins, which only function in passive transport, form hydrophilic pores  
across the membrane. When the pores open, specific solutes, such as inorganic ions, pass through the  
membrane and down the electrochemical gradient of the solute.

30 Transport proteins play roles in antibiotic resistance, toxin secretion, ion balance, synaptic  
neurotransmission, kidney function, intestinal absorption, tumor growth, and other diverse cell  
functions (Griffith, J. and C. Sansom (1998) The Transporter Facts Book, Academic Press, San Diego  
CA, pp. 3-29). A variety of human inherited diseases are caused by mutation of transport proteins.  
For example, cystinuria is an inherited disease that results from the inability to transport cystine, the

disulfide-linked dimer of cysteine, from the urine into the blood. Accumulation of cystine in the urine leads to the formation of cystine stones in the kidneys. Also, many transport proteins are composed of subunits that may confer specificity for the tissue in which the transport mechanism functions, and are therefore associated with tissue-specific disorders. Examples of transport proteins include

5 facilitative transporters, the secondary active symporters and antiporters driven by ion gradients, and active ATP binding cassette transporters involved in multiple-drug resistance and targeting of antigenic peptides to MHC Class I molecules, and the E1-E2 cation transport ATPases.

Carrier proteins which transport a single solute from one side of the membrane to the other are called uniporters. In contrast, coupled transporters link the transfer of one solute with

10 simultaneous or sequential transfer of a second solute, either in the same direction (symport) or in the opposite direction (antiport). For example, intestinal and kidney epithelium contains a variety of symporter systems wherein the movement of sodium into the cell down its electrochemical gradient co-transport a second solute into the cell. The sodium gradient that provides the driving force for solute uptake is maintained by the ubiquitous  $\text{Na}^+/\text{K}^+$  ATPase. Sodium-coupled transporters include

15 the mammalian glucose transporter (SGLT1), iodide transporter (NIS), and multivitamin transporter (SMVT). These three transporters have twelve putative transmembrane segments, extracellular glycosylation sites, and cytoplasmically-oriented N- and C-termini. NIS plays a crucial role in the evaluation, diagnosis, and treatment of various thyroid pathologies because it is the molecular basis for radioiodide thyroid-imaging techniques and for specific targeting of radioisotopes to the thyroid

20 gland (Levy, O. et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:5568-5573). SMVT is expressed in the intestinal mucosa, kidney, and placenta, and is implicated in the transport of the water-soluble vitamins, e.g., biotin and pantothenate (Prasad, P.D. et al. (1998) *J. Biol. Chem.* 273:7501-7506).

The largest and most diverse family of transport proteins is the ATP-binding cassette (ABC) transporters. As a family, ABC transporters can transport substances that differ markedly in chemical

25 structure and size, ranging from small molecules such as ions, sugars, amino acids, peptides, and phospholipids, to lipopeptides, large proteins, and complex hydrophobic drugs. Each ABC transporter consists of four modules: two nucleotide-binding domains (NBDs), which hydrolyze ATP to supply the energy required for transport; and two membrane-spanning domains (MSDs), which may form membrane channels. The NBDs consist of approximately two hundred conserved amino

30 acid residues while the MSDs each contain six putative transmembrane segments. (See, e.g., Saurin, W. et al. (1994) *Mol. Microbiol.* 12:993-1004; Shani, N. et al. (1996) *J. Biol. Chem.* 271:8725-8730; Koster, W. and B. Bohm (1992) *Mol. Gen. Genet.* 232:399-407.) The four ABC transporter modules may be encoded by a single gene, as is the case for the cystic fibrosis transmembrane conductance regulator (CFTR), or by separate genes. When encoded by separate genes, each gene product

contains a single NBD and MSD. These "half-molecules" form homo- and heterodimers, such as Tap1 and Tap2, the endoplasmic reticulum-based major histocompatibility (MHC) peptide transport system associated with antigen processing (Androlewicz, M.J. et al. (1994) Proc. Natl. Acad. Sci. USA 91:12716-12720).

- 5        Several genetic diseases are attributed to defects in ABC transporters, including the following diseases and their corresponding proteins: cystic fibrosis (CFTR, an ion channel; Welsh, M.J. and A.E. Smith (1993) Cell 73:1251-1254); X-linked adrenoleukodystrophy, an inborn error of peroxisomal  $\beta$ -oxidation of very long chain fatty acids (adrenoleukodystrophy protein, ALDP); Zellweger syndrome, an inborn error of peroxisome biogenesis (peroxisomal membrane protein-70, PMP70); and hyperinsulinemic hypoglycemia (sulfonyleurea receptor, SUR). The ABC transporters
- 10        known as P-glycoproteins, or multidrug resistance (MDR) proteins, are associated with resistance to a wide range of hydrophobic drugs (MDR1; Gottesman, M.M. and I. Pastan (1993) Annu. Rev. Biochem. 62:385-427) or with phosphatidylcholine transport (MDR2; Ruetz, S. and P. Gros (1994) Cell 77:1071-1081). MDR is common in cancer cells, and contributes to low efficacy or failure of
- 15        chemotherapy (Taglicht, D. and S. Michaelis (1998) Methods Enzymol. 292:131-163). MDR is mediated by transporters, e.g., P-glycoproteins or the multidrug resistance-associated protein MRP, that normally function in the liver, intestines, and kidney to move toxic substances from the cytosol into the bile, intestinal lumen, or urine. In cancerous cells, these transporters extrude
- 20        chemotherapeutic agents into the extracellular space, thereby conferring drug resistance. Recently, an ABC transporter-type protein was isolated from a human leukemia cell line. This transporter, termed the anthracycline resistance associated protein (GI 1279457, SEQ ID NO:42), is overexpressed in a multidrug resistant leukemia cell sub-line, and has sequence homology with other multidrug-resistance associated proteins including MRP (Longhurst, T.J. et al. (1996) Br. J. Cancer 74:1331-1335).
- 25        Transport of fatty acids across the plasma membrane can occur by diffusion, a high capacity, low affinity process. However, under normal physiological conditions a significant fraction of fatty acid transport appears to occur via a high affinity, low capacity protein-mediated transport process. Fatty acid transport protein (FATP), an integral membrane protein with four transmembrane
- 30        segments, is expressed in tissues exhibiting high levels of plasma membrane fatty acid flux, such as muscle, heart, and adipose. Expression of FATP is upregulated in 3T3-L1 cells during adipose conversion, and expression in COS7 fibroblasts elevates the cells' uptake of long-chain fatty acids. Expression studies suggest a role for FATP in lipid metabolism, obesity, and type II diabetes mellitus (Hui, T.Y. et al. (1998) J. Biol. Chem. 273:27420-27429).

E1-E2 (or P-type) ATPases constitute a superfamily of cation transporters present in both

prokaryotes and eukaryotes that mediate membrane flux of all biologically relevant cations. These ATPases are postulated to exist in two different conformational states, designated E1 and E2, during the course of the ATP hydrolysis reaction, and to conserve the energy from ATP hydrolysis in the form of an acyl phosphate, primarily an aspartyl phosphate. Members of this family are divided into  
5 four major groups; the  $\text{Ca}^{+2}$ -transporting ATPases,  $\text{Na}^{+}/\text{K}^{+}$ -and gastric  $\text{H}^{+}/\text{K}^{+}$ -transporting ATPases, plasma membrane  $\text{H}^{+}$ -transporting ATPases (proton pumps), and the bacterial P-type ATPases (BLOCKS: BL00154, P-type cation-transporting ATPase superfamily signature).

The metabolism of amino acids is complex and highly regulated. While cells are capable of creating most amino acids de novo, the import of amino acids into cells via specific amino acid  
10 permease proteins is vital for maintaining the appropriate and complete availability of all necessary amino acids. This is particularly important during cell proliferation and differentiation. In addition to their role as protein building blocks, amino acids also serve as precursors for a variety of other important macromolecules. For example, the hormone thyroxine, the pigment melanin, and the neurotransmitters histamine, epinephrine, and serotonin are produced from various amino acid  
15 precursors, including histidine, tyrosine, and tryptophan. A component of sphingolipid formation, sphingosine, is derived from serine. Porphyrin rings, which are components of heme molecules, use glycine as a nitrogen donor. Significant portions of the ring structures of purines and pyrimidines, components of nucleic acids, are formed from the breakdown of numerous amino acids. Amino acids are also important in energy metabolism. Unlike fatty acids and glucose, amino acids cannot be  
20 stored in the cell, so excess amino acids are fed into the citric acid cycle to produce energy molecules including fatty acids, ketone bodies, and glucose. Thus, precise control of amino acid metabolism is extremely important to both proliferating and non-proliferating cells.

The E16 gene, cloned from human peripheral blood lymphocytes, encodes a 241 amino acid integral membrane protein with multiple predicted transmembrane domains (Gaugitsch, H.W. et al.  
25 (1992) J. Biol. Chem. 267:11267-11273). E16 gene expression is closely linked to cellular activation and division. In myeloid and lymphoid cells, E16 transcripts are rapidly induced and rapidly degraded after stimulation. This pattern of expression resembles the kinetics seen for proto-oncogenes and lymphokines in the T cell system. Elevated levels of E16 expression were detected in colonic, gastric, and breast adenocarcinomas, and in lymphoma, while little or no E16 expression was  
30 detected in normal (non-cancerous) human tissues such as adult brain, lung, liver, colon, esophagus, stomach, or kidney, nor in four-month fetal brain, lung, liver, or kidney (Wolf, D.A. et al. (1996) Cancer Res. 56:5012-5022; Gaugitsch et al., supra). E16 was detected in every cell line tested. Its presence in rapidly dividing cell lines and its absence in human tissues with low proliferative potential suggest that E16 is directly involved in the cell division process, where it helps provide important

building blocks for energy metabolism, biochemical synthetic pathways, and protein synthesis.

Post-translational modification of polypeptides occurs in the lumen of the Golgi apparatus. Such modifications include, for example, the addition of sugar molecules by enzymes such as N-acetylglucosaminyltransferase, to produce glycoproteins. The sugar-donating molecules in this reaction are typically nucleotide sugars, such as uridine diphosphate-galactose (UDP-Gal). UDP-Gal and other nucleotide sugars are transported from the cytosol into the Golgi apparatus by specific transporter molecules. The availability of these nucleotide sugars can regulate which glycoproteins are synthesized, and therefore has a significant impact on cellular function (Toma, L. et al. (1996) J. Biol. Chem. 271:3897-3901; Guillen, E. et al. (1998) Proc. Natl. Acad. Sci. USA 95:7888-7892).

The discovery of new membrane transport proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

#### SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, membrane transport proteins, referred to collectively as "MTRP" and individually as "MTRP-1," "MTRP-2," "MTRP-3," "MTRP-4," "MTRP-5," "MTRP-6," "MTRP-7," "MTRP-8," "MTRP-9," "MTRP-10," "MTRP-11," "MTRP-12," "MTRP-13," "MTRP-14," "MTRP-15," "MTRP-16," and "MTRP-17." In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes a polypeptide comprising an amino acid sequence that differs by one or more conservative amino acid substitutions from an amino acid sequence selected from the group consisting of SEQ ID NO:1-17.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The

invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

5 The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of: (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

10 The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention also provides an isolated and  
15 purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group  
20 consisting of SEQ ID NO:1-17. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing a polynucleotide of the invention under conditions suitable for the expression of the polypeptide; and (b) recovering the  
25 polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from  
30 the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially



purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

### BRIEF DESCRIPTION OF THE FIGURES AND TABLES

Figures 1A, 1B, 1C, and 1D show the amino acid sequence alignment between MTRP-3 (Incyte Clone ID 1720440; SEQ ID NO:3) and mouse fatty acid transport protein (GI 2612939; SEQ ID NO:35), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 2A, 2B, 2C, and 2D show the amino acid sequence alignment between MTRP-4 (Incyte Clone ID 2274290; SEQ ID NO:4) and Schistosoma mansoni SMDR1 (GI 425474; SEQ ID NO:36), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Figures 3A, 3B, 3C, and 3D show the amino acid sequence alignment between MTRP-5 (Incyte Clone ID 2740029; SEQ ID NO:5) and rat sodium-dependent multivitamin transporter (GI 3015617; SEQ ID NO:37), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding MTRP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of MTRP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze MTRP, along with applicable descriptions, references, and threshold parameters.

### DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

#### DEFINITIONS

"MTRP" refers to the amino acid sequences of substantially purified MTRP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of MTRP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

An "allelic variant" is an alternative form of the gene encoding MTRP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding MTRP include those sequences with deletions,

insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as MTRP or a polypeptide with at least one functional characteristic of MTRP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding MTRP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding MTRP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent MTRP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of MTRP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of MTRP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind MTRP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the

translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

5       The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen  
10       used to elicit the immune response) for binding to an antibody.

      The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes  
15       and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

      The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic MTRP, or of any oligopeptide thereof, to induce a  
20       specific immune response in appropriate animals or cells and to bind with specific antibodies.

      The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that  
25       total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

30       A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding MTRP or fragments of MTRP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be

associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
15	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
20	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
	His	Asn, Arg, Gln, Glu
25	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
30	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
	Val	Ile, Leu, Thr

35

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

40 A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of MTRP or the polynucleotide encoding MTRP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:18-34 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:18-34, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:18-34 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:18-34 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:18-34 and the region of SEQ ID NO:18-34 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-17 is encoded by a fragment of SEQ ID NO:18-34. A fragment of SEQ ID NO:1-17 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-17. For example, a fragment of SEQ ID NO:1-17 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-17. The precise length of a fragment of SEQ ID NO:1-17 and the region of SEQ ID NO:1-17 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially

complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2

Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to  
5 compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Reward for match: 1*

*Penalty for mismatch: -2*

10 *Open Gap: 5 and Extension Gap: 2 penalties*

*Gap x drop-off: 50*

*Expect: 10*

*Word Size: 11*

*Filter: on*

15 Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported  
20 by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid  
25 sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative  
30 substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of



polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

- 5 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Open Gap: 11 and Extension Gap: 1 penalties*

- 10 *Gap x drop-off: 50*

*Expect: 10*

*Word Size: 3*

*Filter: on*

- Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.
- 20

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

- The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.
- 25

- "Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and
- 30

may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

5 Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and  
10 conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour.  
15 Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for  
20 RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid  
25 sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g.,  $C_0t$  or  $R_0t$  analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

30 The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect

cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

5 The term "modulate" refers to a change in the activity of MTRP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of MTRP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or  
10 synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding  
15 sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition.  
20 PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding MTRP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule.

25 Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

30 Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the

specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology, 5 Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such 10 purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of 15 Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of 20 oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned 25 nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide 30 selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques

such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to  
5 transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic  
10 acids encoding MTRP, or fragments thereof, or MTRP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or  
15 synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

20 The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by  
25 different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

30 "Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection,

electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

5 A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or  
10 greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the  
15 reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The  
20 presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-  
25 1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

### THE INVENTION

The invention is based on the discovery of new human membrane transport proteins (MTRP),  
30 the polynucleotides encoding MTRP, and the use of these compositions for the diagnosis, treatment, or prevention of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding MTRP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide

and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each MTRP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each MTRP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

As shown in Figures 1A, 1B, 1C, and 1D, MTRP-3 has chemical and structural similarity with mouse fatty acid transport protein (FATP; GI 2612939; SEQ ID NO:35). In particular, MTRP-3 and FATP share 65% identity. As shown in Figures 2A, 2B, 2C, and 2D, MTRP-4 has chemical and structural similarity with *Schistosoma mansoni* ATP-binding cassette family protein, SMDR-1 (GI 425474; SEQ ID NO:36). In particular, MTRP-4 and SMDR-1 share 38% identity. As shown in Figures 3A, 3B, 3C, and 3D, MTRP-5 has chemical and structural similarity with rat sodium-dependent multivitamin transporter (SMVT; GI 3015617; SEQ ID NO:37). In particular, MTRP-5 and SMVT share 82% identity.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding MTRP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists tissue categories which express MTRP as a fraction of total tissues expressing MTRP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing MTRP as a fraction of total tissues expressing MTRP. Column 4 lists the vectors used to subclone each cDNA library.

Of particular note are the expression patterns of SEQ ID NO:30 and SEQ ID NO:31. SEQ ID NO:30 is expressed in only five libraries, of which at least four (80%) are associated with cell proliferation and at least one (20%) with inflammation. Two (40%) of the five libraries are associated with cardiovascular tissue, and one each (20%) with gastrointestinal, nervous, and reproductive tissues. SEQ ID NO:31 is expressed in only four libraries, of which at least three (75%) are associated with cell proliferation and at least two (50%) with inflammation or the immune response.

Two (50%) of the four libraries are associated with hematopoietic/immune tissue, and one each (25%) with cardiovascular and reproductive tissues.

The following fragments of the nucleotide sequences encoding MTRP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:18-34 and to distinguish between SEQ ID NO:18-34 and related polynucleotide sequences. The useful fragments include the fragment of SEQ ID NO:18 from about nucleotide 110 to about nucleotide 154; the fragment of SEQ ID NO:19 from about nucleotide 759 to about nucleotide 839; the fragment of SEQ ID NO:20 from about nucleotide 1531 to about nucleotide 1578; the fragment of SEQ ID NO:21 from about nucleotide 538 to about nucleotide 597; the fragment of SEQ ID NO:22 from about nucleotide 2241 to about nucleotide 2294; the fragment of SEQ ID NO:23 from about nucleotide 116 to about nucleotide 145; the fragment of SEQ ID NO:24 from about nucleotide 60 to about nucleotide 89; the fragment of SEQ ID NO:25 from about nucleotide 160 to about nucleotide 189; the fragment of SEQ ID NO:26 from about nucleotide 763 to about nucleotide 792; the fragment of SEQ ID NO:27 from about nucleotide 43 to about nucleotide 72; the fragment of SEQ ID NO:28 from about nucleotide 361 to about nucleotide 405; the fragment of SEQ ID NO:29 from about nucleotide 35 to about nucleotide 79; the fragment of SEQ ID NO:30 from about nucleotide 206 to about nucleotide 250; the fragment of SEQ ID NO:31 from about nucleotide 71 to about nucleotide 115; the fragment of SEQ ID NO:32 from about nucleotide 161 to about nucleotide 205; the fragment of SEQ ID NO:33 from about nucleotide 364 to about nucleotide 408; and the fragment of SEQ ID NO:34 from about nucleotide 18 to about nucleotide 62. The polypeptides encoded by the specified fragments of SEQ ID NO:20-30 and SEQ ID NO:32-34 are useful, for example, as immunogenic peptides.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The invention also encompasses MTRP variants. A preferred MTRP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the MTRP amino acid sequence, and which contains at least one functional or structural characteristic of MTRP.

The invention also encompasses polynucleotides which encode MTRP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34, which encodes MTRP.

The invention also encompasses a variant of a polynucleotide sequence encoding MTRP. In particular, such a variant polynucleotide sequence will have at least about 75%, or alternatively at



least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding MTRP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34 which has at least about 75%, or alternatively at least about 85%, or even at least about 5 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:18-34. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of MTRP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding MTRP, some bearing minimal 10 similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring MTRP, and all such variations are to be considered as 15 being specifically disclosed.

Although nucleotide sequences which encode MTRP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring MTRP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding MTRP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally 20 occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding MTRP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater 25 half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode MTRP and MTRP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce 30 mutations into a sequence encoding MTRP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:18-34 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.*

152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding MTRP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060.) Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National

Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been  
5 size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze  
10 the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process  
15 from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode MTRP may be cloned in recombinant DNA molecules that direct expression of MTRP,  
20 or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express MTRP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter MTRP-encoding sequences for a variety of purposes including, but  
25 not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

30 In another embodiment, sequences encoding MTRP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, MTRP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g.,

Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of MTRP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5       The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

10       In order to express a biologically active MTRP, the nucleotide sequences encoding MTRP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences  
15       encoding MTRP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding MTRP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding MTRP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals  
20       may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

25       Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding MTRP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding MTRP. These include, but are not limited to, microorganisms such as bacteria transformed

with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or  
5 animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding MTRP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding MTRP can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1  
10 plasmid (Life Technologies). Ligation of sequences encoding MTRP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of  
15 nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of MTRP are needed, e.g. for the production of antibodies, vectors which direct high level expression of MTRP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of MTRP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH  
20 promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

25 Plant systems may also be used for expression of MTRP. Transcription of sequences encoding MTRP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.)  
30 These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases

where an adenovirus is used as an expression vector, sequences encoding MTRP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses MTRP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of MTRP in cell lines is preferred. For example, sequences encoding MTRP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*<sup>-</sup> and *apv*<sup>-</sup> cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech),  $\beta$  glucuronidase and its substrate  $\beta$ -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to

quantify the amount of transient or stable protein expression attributable to a specific vector system.  
(See, e.g., Rhodes, C.A. (1995) *Methods Mol. Biol.* 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding MTRP is inserted within a marker gene sequence, transformed cells containing  
5 sequences encoding MTRP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding MTRP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

10 In general, host cells that contain the nucleic acid sequence encoding MTRP and that express MTRP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

15 Immunological methods for detecting and measuring the expression of MTRP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on MTRP is preferred, but a  
20 competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

25 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding MTRP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding MTRP, or any fragments thereof, may be cloned into a vector  
30 for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding MTRP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein  
5 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode MTRP may be designed to contain signal sequences which direct secretion of MTRP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the  
10 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for  
15 post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding MTRP may be ligated to a heterologous sequence resulting in translation of a  
20 fusion protein in any of the aforementioned host systems. For example, a chimeric MTRP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of MTRP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST),  
25 maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity  
30 purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the MTRP encoding sequence and the heterologous protein sequence, so that MTRP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of



fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled MTRP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

Fragments of MTRP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of MTRP may be synthesized separately and then combined to produce the full length molecule.

### THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of MTRP and membrane transport proteins, including amino acid transporters, ABC transporters, nucleotide-sugar transporters, transmembrane carrier proteins, and ATP-dependent transporter proteins. In addition, the expression of MTRP is closely associated with nervous, reproductive, and gastrointestinal tissues; cancer and other cell proliferative conditions; and with inflammation and the immune response. Therefore, MTRP appears to play a role in membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer. In the treatment of disorders associated with increased MTRP expression or activity, it is desirable to decrease the expression or activity of MTRP. In the treatment of disorders associated with decreased MTRP expression or activity, it is desirable to increase the expression or activity of MTRP.

Therefore, in one embodiment, MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus,

- diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina,
- 5 bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and
- 10 schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as
- 15 acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia
- 20 with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic
- 25 lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis,
- 30 primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified MTRP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of MTRP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those listed above.

In a further embodiment, an antagonist of MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP. Examples of such disorders include, but are not limited to, those membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer described above. In one aspect, an antibody which specifically binds MTRP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express MTRP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of MTRP may be produced using methods which are generally known in the art. In particular, purified MTRP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind MTRP. Antibodies to MTRP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with MTRP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral  
5 gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to MTRP have an amino acid sequence consisting of at least about 5 amino acids, and generally will  
10 consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of MTRP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

15 Monoclonal antibodies to MTRP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and  
20 Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda,  
25 S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce MTRP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

30 Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for MTRP may also be generated.

For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between MTRP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering MTRP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for MTRP. Affinity is expressed as an association constant,  $K_a$ , which is defined as the molar concentration of MTRP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The  $K_a$  determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple MTRP epitopes, represents the average affinity, or avidity, of the antibodies for MTRP. The  $K_a$  determined for a preparation of monoclonal antibodies, which are monospecific for a particular MTRP epitope, represents a true measure of affinity. High-affinity antibody preparations with  $K_a$  ranging from about  $10^9$  to  $10^{12}$  L/mole are preferred for use in immunoassays in which the MTRP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with  $K_a$  ranging from about  $10^6$  to  $10^7$  L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of MTRP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of MTRP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding MTRP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding MTRP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with  
5 sequences complementary to polynucleotides encoding MTRP. Thus, complementary molecules or fragments may be used to modulate MTRP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding MTRP.

10 Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding MTRP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

15 Genes encoding MTRP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding MTRP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more  
20 with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding MTRP. Oligonucleotides derived from the transcription  
25 initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber,  
30 B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme

molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding MTRP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding MTRP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of MTRP, antibodies to MTRP, and mimetics, agonists, antagonists, or inhibitors of MTRP. The compositions  
5 may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any  
10 number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing  
15 of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration.  
20 Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable  
25 excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof,  
30 such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to



characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or  
5 starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's  
10 solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic  
15 amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

20 The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic  
25 acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate  
30 container and labeled for treatment of an indicated condition. For administration of MTRP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for

5 administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example MTRP or fragments thereof, antibodies of MTRP, and agonists, antagonists or inhibitors of MTRP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by  
10 calculating the  $ED_{50}$  (the dose therapeutically effective in 50% of the population) or  $LD_{50}$  (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the  $LD_{50}/ED_{50}$  ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such  
15 compositions is preferably within a range of circulating concentrations that includes the  $ED_{50}$  with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the  
20 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular  
25 formulation.

Normal dosage amounts may vary from about 0.1  $\mu\text{g}$  to 100,000  $\mu\text{g}$ , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their  
30 inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

#### DIAGNOSTICS

In another embodiment, antibodies which specifically bind MTRP may be used for the diagnosis of disorders characterized by expression of MTRP, or in assays to monitor patients being

5 treated with MTRP or agonists, antagonists, or inhibitors of MTRP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for MTRP include methods which utilize the antibody and a label to detect MTRP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

10 A variety of protocols for measuring MTRP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of MTRP expression. Normal or standard values for MTRP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to MTRP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of MTRP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

15 In another embodiment of the invention, the polynucleotides encoding MTRP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of MTRP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of MTRP, and to monitor regulation of MTRP levels during therapeutic intervention.

20 In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding MTRP or closely related molecules may be used to identify nucleic acid sequences which encode MTRP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding MTRP, allelic variants, or related sequences.

25 Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the MTRP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:18-34 or from genomic sequences including promoters, enhancers, and introns of the MTRP gene.

Means for producing specific hybridization probes for DNAs encoding MTRP include the cloning of polynucleotide sequences encoding MTRP or MTRP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may

be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

- 5 Polynucleotide sequences encoding MTRP may be used for the diagnosis of disorders associated with expression of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial
- 10 hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's
- 15 muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus, diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina,
- 20 bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and
- 25 schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as
- 30 acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia

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with lymphocytotoxins; erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding MTRP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered MTRP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding MTRP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding MTRP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding MTRP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of MTRP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding MTRP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from

normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

5        Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

10        With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development  
15 or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding MTRP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding MTRP, or a fragment of a polynucleotide complementary to the polynucleotide encoding  
20 MTRP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of MTRP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from  
25 standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

30        In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and

monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. 5 (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding MTRP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to 10 artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome 15 mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding MTRP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. 20 The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, 25 may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping 30 to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, MTRP, its catalytic or immunogenic fragments, or

oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between MTRP and the agent being tested may be measured.

5 Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with MTRP, or fragments thereof, and washed. Bound MTRP is then detected by methods well known in the art. Purified MTRP can  
10 also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding MTRP specifically compete with a test compound for binding MTRP.  
15 In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with MTRP.

In additional embodiments, the nucleotide sequences which encode MTRP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such  
20 properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific  
25 embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No. PF-0633 P, filed November 4, 1998], U.S. Ser. No. [Attorney Docket No. PF-0645 P, filed November 24, 1998], U.S. Ser. No. [Attorney Docket No. PF-0657 P, filed December 22, 1998], and U.S. Ser. No. 60/121,896, are hereby expressly incorporated  
30 by reference.

## EXAMPLES

### I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some



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tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 $\alpha$ , DH10B, or ElectroMAX DH10B from Life Technologies.

## II. Isolation of cDNA Clones

Plasmids were recovered from host cells by *in vivo* excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a

high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

### III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, *supra*, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA

sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire  
5 annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying  
10 against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and  
15 amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:18-34. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

#### IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a  
20 gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This  
25 analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

30 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding MTRP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

10 **V. Extension of MTRP Encoding Polynucleotides**

The full length nucleic acid sequences of SEQ ID NO:18-34 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using  
15 OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one  
20 extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ ,  $(NH_4)_2SO_4$ , and  $\beta$ -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme  
25 (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;  
30 Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II

(Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

5        The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones  
10        were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

15        The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA  
20        recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

      In like manner, the nucleotide sequences of SEQ ID NO:18-34 are used to obtain 5'  
25        regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

#### VI.     Labeling and Use of Individual Hybridization Probes

      Hybridization probes derived from SEQ ID NO:18-34 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base  
30        pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ -<sup>32</sup>P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a

SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing  $10^7$  counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

5        The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and  
10 compared.

#### VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal,  
15 UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned  
20 images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or  
25 selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by  
30 procedures described above.

#### VIII. Complementary Polynucleotides

Sequences complementary to the MTRP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring MTRP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same

procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of MTRP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the MTRP-encoding transcript.

#### IX. Expression of MTRP

Expression and purification of MTRP is achieved using bacterial or virus-based expression systems. For expression of MTRP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express MTRP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of MTRP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding MTRP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, MTRP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from MTRP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified MTRP obtained by these methods can be used directly in the

following activity assay.

#### X. Demonstration of MTRP Activity

ATPase activity associated with MTRP can be measured by hydrolysis of radiolabeled ATP- $[\gamma\text{-}^{32}\text{P}]$ , separation of the hydrolysis products by chromatographic methods, and quantitation of the recovered  $^{32}\text{P}$  using a scintillation counter. The reaction mixture contains ATP- $[\gamma\text{-}^{32}\text{P}]$  and varying amounts of MTRP in a suitable buffer incubated at 37°C for a suitable period of time. The reaction is terminated by acid precipitation with trichloroacetic acid and then neutralized with base, and an aliquot of the reaction mixture is subjected to membrane or filter paper-based chromatography to separate the reaction products. The amount of  $^{32}\text{P}$  liberated is counted in a scintillation counter. The amount of radioactivity recovered is proportional to the ATPase activity of MTRP in the assay.

MTRP transport activity is assayed by measuring uptake of labeled substrates into *Xenopus laevis* oocytes. Oocytes at stages V and VI are injected with MTRP mRNA (10 ng per oocyte) and incubated for 3 days at 18°C in OR2 medium (82.5mM NaCl, 2.5 mM KCl, 1mM CaCl<sub>2</sub>, 1mM MgCl<sub>2</sub>, 1mM Na<sub>2</sub>HPO<sub>4</sub>, 5 mM Hepes, 3.8 mM NaOH, 50µg/ml gentamycin, pH 7.8) to allow expression of MTRP protein. Oocytes are then transferred to standard uptake medium (100mM NaCl, 2 mM KCl, 1mM CaCl<sub>2</sub>, 1mM MgCl<sub>2</sub>, 10 mM Hepes/Tris, pH 7.5). Uptake of various substrates (e.g., amino acids, sugars, drugs, and neurotransmitters) is initiated by adding a  $^3\text{H}$ -labeled substrate to the oocytes. After 30 minutes of incubation, uptake is terminated by washing the oocytes three times in Na<sup>+</sup>-free medium. Incorporation of  $^3\text{H}$  is measured, and compared with controls. MTRP transport activity is proportional to the level of internalized  $^3\text{H}$ -labeled substrate.

#### XI. Functional Assays

MTRP function is assessed by expressing the sequences encoding MTRP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of



fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of MTRP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding MTRP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding MTRP and other genes of interest can be analyzed by northern analysis or microarray techniques.

## **XII. Production of MTRP Specific Antibodies**

MTRP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the MTRP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-MTRP activity by, for example, binding the peptide or MTRP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

## **XIII. Purification of Naturally Occurring MTRP Using Specific Antibodies**

Naturally occurring or recombinant MTRP is substantially purified by immunoaffinity

chromatography using antibodies specific for MTRP. An immunoaffinity column is constructed by covalently coupling anti-MTRP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

- 5 Media containing MTRP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of MTRP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/MTRP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and MTRP is collected.

10 **XIV. Identification of Molecules Which Interact with MTRP**

- MTRP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled MTRP, washed, and any wells with labeled MTRP complex are assayed. Data obtained using different concentrations of MTRP are used to calculate values for the number, affinity, and association of MTRP with the candidate molecules.
- 15

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.

- 20 Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	18	961344	BRSTTUT03	642329R1 (BRSTNOT03), 961344H1 (BRSTTUT03), 3149970H1 (ADREN04), 3255621H1 (OVRTUT01), 4265773H1 (KIDN032), 4641320H1 (FROSTMT03), 4875558H1 (COLN0T01)
2	19	3128782	LUNGTUT12	148511X20R1 (FIBRNGT01), 580891H1 (BRAVXT05), 1304328F1 (PLACNOT02), 1469890T6 (PANCNOT02), 1799816T6 (COLN0T27), 1985910R6 (LUNGAST01), 2722244F6 (LUNGTUT10), 3128782F6 (LUNGTUT12), 3128782H1 (LUNGTUT12), 3276993F6 (PROSBPT06), SBWA03256F1
3	20	1720440	BLADNOT06	744485R1 (BRAITUT01), 859118R1 (BRAITUT03), 944049T1 (ADREN0T03), 1432755R1 (BEPIN01), 1720440H1 (BLADNOT06), 1808737X11C1 (PROSTUT12), 1812106F6 (PROSTUT12), 2192988F6 (THYRTUT03), 2192988X13F1 (THYRTUT03), 2192988X14F1 (THYRTUT03), 3384757H1 (ESCGNCT04)
4	21	2274290	PROSNON01	1732422F6 (BRSTTUT08), 2098563H1 (BRAITUT02), 2274290H1 (PROSNON01), 2274290X326D2 (PROSNON01), 2598580F6 (UTRSNOT10), 2779864F6 (OVRTUT03), 2864759F6 (KIDN0T20), 2864759T6 (KIDN0T20), 3221871H1 (COLN0N03)
5	22	2740029	BRSTTUT14	966363H1 (BRSTNOT05), 1000112R1 (BRSTNOT03), 1647057F6 (PROSTUT09), 2740029H1 (BRSTTUT14), 2740029X309F1 (BRSTTUT14), 2740029X321F1 (BRSTTUT14), 5068692H1 (PANCNOT23), 5193978H1 (LUNLTUT04), SBOA03895D1
6	23	2414415	HNT3AZT01	1508631H1 (LUNGNOT14), 1596418F1 (BRAINOT14), 2414415F6 (HNT3AZT01), 2414415H1 (HNT3AZT01), 2414415X300D1 (HNT3AZT01), 2902794H1 (DRGCNOT01), 3080373H1 (BRAIUNT01), 3554689H1 (SYN0T01), 3881949F6 (SPLN0T11), 4996983H1 (MYEPTXT02)
7	24	2466714	THYRN0T08	627910R6 (KIDN0T05), 2358261R6 (LUNGFET05), 2358464F6 (LUNGFET05), 2466714H1 (THYRN0T08), 2726053F6 (OVRTUT05), 3845383H1 (DENDNOT01), 4228854H1 (BRAMDIT01)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	25	2617942	GBLANCT01	1311045F6 (COLNFET02), 1375061F6 (LUNGNOT10), 1580318F6 (DUODNOT01), 2016443F6 (ENDCNOT03), 2617942F6 (GBLANOT01), 2617942H1 (GBLANOT01), 2703625H1 (OVRTUT10)
9	26	2945431	BRAITUT23	782666T6 (MYOMNOT01), 2715384T6 (THYRNOT09), 2945431F6 (BRAITUT23), 2945431H1 (BRAITUT23), 4114919F6 (UTRSTUT07)
10	27	4074113	KIDNNOT26	1754278T6 (LIVRTUT01), 1830341T6 (THP1AZT01), 2122328T6 (BRSTNOT07), 4074113F6 (KIDNNOT26), 4074113H1 (KIDNNOT26)
11	28	1413743	BRAINOT12	1413743H1 (BRAINOT12), 2643096F6 (LUNGTUT08), SBWA04580V1, SBWA04306V1, SEWA00027V1, SBWA00447V1, SBWA00075V1, SBWA03280V1, SBWA00778V1
12	29	1733477	BRSTTUT08	1733477H1 (BRSTTUT08), 1733477F6 (BRSTTUT08), 3346594F6 (BRAITUT24), 1696051F6 (COLNNOT23), SAFC01922F1, 3234341F6 (COLNUCT03), 2634476T6 (COLNTUT15), SBGA03249F1
13	30	2641908	LUNGTUT08	2641908H1 (LUNGTUT08), SASA01215F1, SASB01010F1, SASB01616F1, SASA03523F1
14	31	2656554	LUNGTUT09	2656554H1 (LUNGTUT09), 2656554F6 (LUNGTUT09), 2656554T6 (LUNGTUT09)
15	32	2719228	THYRNOT09	2719228H1 (THYRNOT09), 2719228F6 (THYRNOT09), 532553H1 (BRAINOT03), 1626110F6 (COLNPOT01), 1626488F6 (COLNPOT01), 2100947R6 (BRAITUT02), SBGA05174F1
16	33	3657824	ENDPNOT02	3657824H1 (ENDPNOT02), 2450345F6 (ENDANOT01), 2756555H1 (THP1AZS08), SCBA01425V1, 2394519T6 (THP1AZT01)
17	34	5378485	BRAXNOT01	5378485H1 (BRAXNOT01), SCAA06347V1, 1570276F1 (UTRSTNOT05)

Table 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/Homologies	Analytical Methods
1	384	S375 S34 T33 T89 T102 S161 S246 T298		E1-E2 ATPase signatures: R85-D115, T106-I128 P-type cation transporter signature: I109-I128 Transmembrane domains: I330-W351, L271-I288	E1-E2 ATPase [Mus musculus] (GI 2944187)	BLAST BLOCKS MOTIFS PFAM PRINTS
2	846	T80 S106 S22 T40 T109 S110 S141 S229 S245 S255 S288 T408 T614 T679 T707 S819 S24 S274 S293 T386 T450 T536 S568 T581 T610 T673	N301	ABC transporter signatures: F453-L467, G330-Q525, D652-Q816, L744-A758 ATP-binding (P-loop) domains: G337-T344, G659-S666	ABC transporter protein isoform [Homo sapiens] (GI 2522534)	BLAST BLOCKS MOTIFS PFAM PRINTS ProfileScan SPScan
3	511	S183 S99 S385 T387 T39 T106 S240 T376 T461 Y111 Y151 Y194 Y353	N195 N238 N258 N383	AMP-binding enzyme motif: R4-V404 AMP-binding domain signature: K91-M144 Lipocalin signature: E2-M14	Fatty acid transport protein [Homo sapiens] (GI 4206376)  Fatty acid transport protein [Mus musculus] (GI 2612939)	BLAST MOTIFS PFAM PRINTS ProfileScan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
4	718	S303 T224 T390 S501 T547 S560 S579 S623 T675 S248 S274 T326 S629 T655	N176 N229 N410	ABC transporter domain: L595-L609 ABC transporter family signatures: G483-V499, L595-D626 ABC transporter transmembrane domain: L128-M408 ABC transporter nucleotide binding domain: G483-G668 ATP/GTP-binding site motif A: G490-T497 Transmembrane domain: F123-V144	ABC transporter protein [Homo sapiens] (GI 4321407)  SMDR1 [Schistosoma mansoni] (GI 425474)	BLAST BLOCKS MOTIFS PFAM HMM
5	635	S25 T55 S128 T172 S242 S284 T378 T140 S222 S283 T286 T549	N138 N489 N498 N534	Sodium:solute symporter family signature: M61-A467, N169-A216, T172-V217, G353-I383, I430-A467  Transmembrane domains: M27-Y45, F256-A276, I430-F448, V458-G480	Sodium:solute symporter [Homo sapiens] (GI 4884550)	BLAST BLOCKS PFAM ProfileScan HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
6	535	T11 S61 S103 S179 S292 T305 S337 T363 S487 S502 Y109		Amino acid permeases signature: L36-K474 (from PFAM) Transmembrane domains: L76-L96, K111-Y131, S159-N176, I189-V207, N264-Y287, I422-F449, I451-W469	SLC7A8 [Homo sapiens] (GI 4581470)  Amino acid transporter (GI 3639058, SEQ ID NO:38)	BLAST BLOCKS MOTIFS PFAM
7	456	T106 S107 S215 S277 T306 T331 S419 S425		Aromatic amino acid permease signature: N53-S98 (from BLOCKS) Transmembrane domains: F47-V69, Y68-L88, T169-L191, L197-I216, S366-Y387, M330-I347, F432-I454	Aromatic amino acid transporter (GI 1840045, SEQ ID NO:39)	BLAST BLOCKS MOTIFS
8	325	T23 T29 S65 T84 S106 S133 S160		Transmembrane domains: I209-D227, I284-T307	UDP-N-acetylglucosamine transporter [Canis familiaris] (GI 3298605)	BLAST MOTIFS
9	178	S4 T22 S132 T151		ABC transporters signature: S2-G141 (from PFAM)	ABC transporter (GI 3335175, SEQ ID NO:41)	BLAST BLOCKS MOTIFS PFAM Profilescan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
10	255	T89 S107 S214		ABC transporters signature: Q45-G227 (from PFAM)	Anthracycline resistance-associated protein (ABC transporter; GI 1279457, SEQ ID NO:42)	BLAST BLOCKS MOTIFS PFAM Profilescan
11	462	T179 S11 S37 T114 S420 T174		Aromatic amino acid permease signatures: F58-A104, A243-F265, L375-K394	Transmembrane transporter [Schizosaccharomyces pombe] (GI 3367790)	BLAST MOTIFS PRINTS
12	758	T174 T251 S376 T615 S616 S633 S678 S713 S733 T138 S574 S603 T656 S687 T726 Y703	N167 N172 N614	Sulfate transporter signature: L198-T508	Transporter [Mus musculus] (GI 5359730)  Transporter [Homo sapiens] (GI 291964)	BLAST MOTIFS PFAM
13	336	T32 S99 S254 T274 S103 T104 T133 S273	N116	Transmembrane domains: L211-G230, A175-L196, W42-F61, F139-F159	Organic anion transporter OATP-B [Homo sapiens] (GI 5006263)	BLAST HMM MOTIFS
14	103	S9 S92 Y14	N81	Transmembrane domain: V22-F41	Similar to Human Na <sup>+</sup> /H <sup>+</sup> exchanger 2 (A57644) [Homo sapiens] (GI 1665827)	BLAST HMM MOTIFS



Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
15	123	S21 S118 T119	N39	Signal peptide: M1-S21	Similar to Sugar transporter [Caenorhabditis elegans] (GI 3878537)	BLAST HMM MOTIFS
16	222	T83 S61 S74			E. coli cation transport protein (GI495778)	BLAST MOTIFS
17	111		N100		Vacuolar proton-ATPase subunit M9.2 [Homo sapiens] (GI 2584789)	BLAST MOTIFS

Table 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
18	Reproductive (0.292) Nervous (0.167) Hematopoietic/Immune (0.125)	Cell proliferative (0.750) Inflammation (0.208)	PSPORT1
19	Reproductive (0.264) Nervous (0.155) Hematopoietic/Immune (0.145)	Cell proliferative (0.691) Inflammation (0.236)	pINCY
20	Reproductive Nervous Gastrointestinal	Cell proliferation (0.66) Inflammation and immune response (0.24)	pINCY
21	Reproductive Nervous Gastrointestinal Hematopoietic/Immune	Cell proliferation (0.73) Inflammation and immune response (0.21)	PSPORT1
22	Nervous Reproductive	Cell proliferation (0.76) Inflammation and immune response (0.33)	pINCY
23	Reproductive (0.333) Nervous (0.296)	Cancer (0.519) Inflammation (0.185)	
24	Reproductive (0.250) Musculoskeletal (0.179) Hematopoietic/Immune (0.143)	Cancer (0.429) Inflammation (0.286)	
25	Reproductive (0.360) Gastrointestinal (0.200) Cardiovascular (0.120)	Cancer (0.520) Inflammation (0.160)	
26	Nervous (0.267) Endocrine (0.133)	Cancer (0.533) Inflammation (0.333)	

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
27	Urologic (0.333) Cardiovascular (0.167) Developmental (0.167)	Cancer (0.667) Inflammation (0.167)	
28	Nervous (0.222) Hematopoietic/Immune (0.185) Reproductive (0.185)	Cell Proliferation (0.481) Inflammation (0.407)	pINCY
29	Gastrointestinal (0.286) Reproductive (0.257) Nervous (0.200)	Cell Proliferation (0.743) Inflammation (0.286)	pINCY
30	Cardiovascular (0.400) Nervous (0.200) Reproductive (0.200) Gastrointestinal (0.200)	Cell Proliferation (0.800) Inflammation (0.200)	pINCY
31	Hematopoietic/Immune (0.500) Reproductive (0.250) Cardiovascular (0.250)	Cell Proliferation (0.750) Inflammation (0.500)	pINCY
32	Gastrointestinal (0.304) Hematopoietic/Immune (0.174) Nervous (0.174)	Cell Proliferation (0.826) Inflammation (0.347)	pINCY
33	Cardiovascular (0.238) Nervous (0.190) Hematopoietic/Immune (0.143)	Cell Proliferation (0.571) Inflammation (0.473)	pINCY
34	Nervous (0.510) Cardiovascular (0.102)	Cell Proliferation (0.612) Inflammation (0.266)	pINCY

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Table 4

Nucleotide SEQ ID NO:	Library	Library Comment
18	BRSTTUT03	Library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
19	LUNGTUT12	Library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure, colon cancer, depressive disorder, and primary liver cancer.
20	BLADNOT06	Library was constructed using RNA isolated from posterior wall bladder tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma on the anterior wall of the bladder and urothelium. Patient history included lung neoplasm. Family history included a malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease, and lung cancer.
21	PROSNON01	Normalized prostate library was constructed from 4.4 million independent clones from a prostate library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
22	BRSTTUT14	Library was constructed using RNA isolated from breast tumor tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. Tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included benign colon neoplasm, hyperlipidemia, cardiac dysrhythmia, and obesity. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer, ovarian cancer, lung cancer, and cerebrovascular disease.
23	HNT3AZT01	Library was constructed using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated for three days with 0.35 micromolar 5-aza-2'-deoxycytidine (A2).
24	THYNOT08	Library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 13-year-old Caucasian female during a complete thyroidectomy. Pathology indicated lymphocytic thyroiditis.
25	GBLANOT01	Library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
26	BRAITUT23	Library was constructed using RNA isolated from left posterior brain tumor tissue removed from a 36-year-old male during a cerebral meninges lesion excision. Pathology indicated meningioma. Family history included malignant skin melanoma, atherosclerotic coronary artery disease, hyperlipidemia, Huntington's chorea, and rheumatoid arthritis.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
27	KIDNNOT26	Library was constructed using RNA isolated from left kidney medulla and cortex tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Patient history included hyperlipidemia, cardiac dysrhythmia, metrorrhagia, cerebrovascular disease, and atherosclerotic coronary artery disease.
28	BRAINOT12	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. The patient presented with intractable convulsive epilepsy. Family history included a cervical neoplasm.
29	BRSTTUT08	Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma (ductal type), with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in-situ, both comedo and non-comedo types. There were also positive estrogen/progesterone receptors and uninvolved tissue showing proliferative changes. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction and atherosclerotic coronary artery disease and type II diabetes.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
30	LUNGTUT08	<p>Library was constructed using RNA isolated from lung tumor tissue removed from a 63-year-old Caucasian male during a right upper lobectomy with fiberoptic bronchoscopy. Pathology indicated a grade 3 adenocarcinoma, forming a mass penetrating the pleura of the right upper lung lobe. The bronchial margin of the resection was free of tumor. The tissue from the superior segment of the right lower lobe lung showed multiple (2) calcified granulomas. Multiple lymph nodes were negative for tumor. In addition, budding yeast forms resembling histoplasma identified in two lymph nodes stained with GMS (silver). Patient history included atherosclerotic coronary artery disease, an acute myocardial infarction, rectal cancer, an asymptomatic abdominal aortic aneurysm, tobacco abuse, and cardiac dysrhythmia. Family history included congestive heart failure, stomach cancer, lung cancer, type II diabetes, atherosclerotic coronary artery disease, and acute myocardial infarction.</p>
31	LUNGTUT09	<p>Library was constructed RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma in the right upper lobe, forming an infiltrating mass involving the bronchus and the surrounding parenchyma. One (of 4) intrapulmonary peribronchial lymph nodes contained a metastatic tumor. An apical cap was identified. One (of 15) right paratracheal lower lymph nodes contained a metastatic tumor. Permanent superior mediastinal sections revealed metastatic squamous cell carcinoma in the lymph nodes. Patient history included of type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use. Family history included brain cancer and atherosclerotic coronary artery disease.</p>

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
32	THYRNOT09	Library was constructed using RNA isolated from diseased thyroid tissue removed from an 18-year-old Caucasian female during an unilateral thyroid lobectomy and regional lymph node excision. Pathology indicated adenomatous goiter. This was associated with a follicular adenoma of the thyroid. The right neck lymph nodes displayed reactive follicular hyperplasia. The patient presented with hypophosphatemia. Patient history included compression of the brain, headache, iron deficiency anemia, active rickets, epidermal nevus syndrome (treated with lasers), and osteitis deformans. Family history included thyroid cancer, type II diabetes, benign hypertension, and nodular lymphoma.
33	ENDPNOT02	Library was constructed using RNA isolated from pulmonary artery endothelial cells removed from a 10-year-old Caucasian male. The cells were treated with TNF alpha and IL-1 beta 10ng/ml each for 20 hours.
34	BRAXNOT01	Library was constructed using RNA isolated from cerebellar tissue removed from a 70-year-old male. Patient history included chronic obstructive airways disease and left ventricular failure.



Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger, and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score $\geq$ GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Philis Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater, Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <u>supra</u> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.
- 5 2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
- 10 4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions  
15 to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
- 20 7. A method for detecting a polynucleotide, the method comprising the steps of:
  - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
  - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
- 25 8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence  
30 selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

- a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and
- b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

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[illegible]

FIGURE 1A

47	F	G	S	E	M	A	S	A	I	C	E	V	H	A	S	L	D	P	S	L	S	L	F	C	S	G	S	W	E	P	1720440
181	Y	G	G	E	M	A	A	V	A	E	V	S	E	Q	L	G	K	S	L	L	K	F	C	S	G	D	L	G	P	GI 2612939	
77	G	A	V	P	P	S	T	E	H	L	D	P	L	L	K	D	A	P	K	-	H	L	P	S	C	P	D	K	G	F	1720440
211	E	S	I	L	P	D	T	Q	L	L	D	P	M	L	A	E	A	P	T	T	P	L	A	Q	A	P	G	K	G	M	GI 2612939
106	T	D	K	L	F	Y	I	Y	T	S	G	T	T	G	L	P	K	A	A	I	V	V	H	S	R	Y	Y	R	M	A	1720440
241	D	D	R	L	F	Y	I	Y	T	S	G	T	T	G	L	P	K	A	A	I	V	V	H	S	R	Y	Y	R	I	A	GI 2612939
136	A	L	V	Y	Y	G	F	R	M	R	P	N	D	I	V	Y	D	C	L	P	L	Y	H	S	A	G	N	I	V	G	1720440
271	A	F	G	H	S	Y	S	M	R	A	A	D	V	L	Y	D	C	L	P	L	Y	H	S	A	G	N	I	M	G	GI 2612939	
166	I	G	Q	C	L	L	H	G	M	T	V	V	I	R	K	K	F	S	A	S	R	F	W	D	D	C	I	K	Y	N	1720440
301	V	G	Q	C	V	I	Y	G	L	T	V	V	L	R	K	K	F	S	A	S	R	F	W	D	D	C	V	K	Y	N	GI 2612939
196	C	T	I	V	Q	Y	I	G	E	L	C	R	Y	L	L	N	Q	P	P	R	E	A	E	N	Q	H	Q	V	R	M	1720440
331	C	T	V	V	Q	Y	I	G	E	I	C	R	Y	L	L	R	Q	P	V	R	D	V	E	Q	R	H	R	V	R	L	GI 2612939

FIGURE 1B

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226	A	L	G	N	G	L	R	Q	S	I	W	T	N	F	S	S	R	F	H	I	P	Q	V	A	E	F	Y	G	A	T	1720440
361	A	V	G	N	G	L	R	P	A	I	W	E	E	F	T	Q	R	F	G	V	P	Q	I	G	E	F	Y	G	A	T	GI 2612939
256	E	C	N	C	S	L	G	N	F	D	S	Q	V	G	A	C	G	F	N	S	R	I	L	S	S	V	Y	P	I	R	1720440
391	E	C	N	C	S	I	A	N	M	D	G	K	V	G	S	C	G	F	N	S	R	I	L	T	H	V	Y	P	I	R	GI 2612939
286	L	V	R	V	N	E	D	T	M	E	L	I	R	G	P	D	G	V	C	I	P	C	Q	P	G	E	P	G	Q	L	1720440
421	L	V	K	V	N	E	D	T	M	E	P	L	R	D	S	E	G	L	C	I	P	C	Q	P	G	E	P	G	L	L	GI 2612939
316	V	G	R	I	I	Q	K	D	P	L	R	R	F	D	G	Y	L	N	Q	G	A	N	N	K	K	I	A	K	D	V	1720440
451	V	G	Q	I	N	Q	Q	D	P	L	R	R	F	D	G	Y	V	S	D	S	A	T	N	K	K	I	A	H	S	V	GI 2612939
346	F	K	K	G	D	Q	A	Y	L	T	G	D	V	L	V	M	D	E	L	G	Y	L	Y	F	R	D	R	T	G	D	1720440
481	F	R	K	G	D	S	A	Y	L	S	G	D	V	L	V	M	D	E	L	G	Y	M	Y	F	R	D	R	S	G	D	GI 2612939
376	T	F	R	W	K	G	E	N	V	S	T	T	E	V	E	G	T	L	S	R	L	L	D	M	A	D	V	A	V	Y	1720440
511	T	F	R	W	R	G	E	N	V	S	T	T	E	V	E	A	V	L	S	R	L	L	G	Q	T	D	V	A	V	Y	GI 2612939

FIGURE 1C

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406	G	V	E	V	P	G	T	E	G	R	A	G	M	A	A	V	A	S	P	T	G	N	C	D	L	E	R	F	A	Q	1720440
541	G	V	A	V	P	G	V	E	G	K	A	G	M	A	A	I	A	D	P	H	S	Q	L	D	P	N	S	M	Y	Q	GI 2612939
436	V	L	E	K	E	L	P	L	Y	A	R	P	I	F	L	R	L	L	P	E	L	H	K	T	G	T	Y	K	F	Q	1720440
571	E	L	Q	K	V	L	A	S	Y	A	R	P	I	F	L	R	L	L	P	Q	V	D	T	T	G	T	F	K	I	Q	GI 2612939
466	K	T	E	L	R	K	E	G	F	D	P	A	I	V	K	D	P	L	F	Y	L	D	A	Q	K	G	R	Y	V	P	1720440
601	K	T	R	L	Q	R	E	G	F	D	P	R	Q	T	S	D	R	L	F	F	L	D	L	K	Q	G	R	Y	V	P	GI 2612939
496	L	D	Q	E	A	Y	S	R	I	Q	A	G	E	E	K	L	1720440														
631	L	D	E	R	V	H	A	R	I	C	A	G	D	F	S	L	GI 2612939														

FIGURE 1D



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1	M	L	V	H	L	F	R	V	G	I	R	G	G	P	F	P	G	R	L	L	P	P	L	R	F	Q	T	F	S	A	2274290
1	M	F	S	A	L	C	R	R	G	-	-	-	-	-	F	L	T	N	K	V	S	Q	F	R	-	S	T	Y	K	C	GI 425474
31	V	R	Y	S	D	G	Y	R	S	S	S	L	L	R	A	V	A	H	L	R	S	Q	L	W	A	H	L	P	R	A	2274290
25	D	H	Y	N	L	K	T	H	I	K	P	L	-	K	C	S	S	S	L	R	L	T	V	G	T	G	L	-	F	I	GI 425474
61	P	L	A	P	R	W	S	P	S	A	W	C	W	V	G	G	A	L	L	G	P	M	V	L	S	K	H	P	H	L	2274290
53	A	L	H	S	K	I	S	P	E	S	R	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Q	T	V	Q	GI 425474
91	C	L	V	A	L	C	E	A	E	E	A	-	-	P	P	A	S	S	T	P	H	V	V	G	S	R	F	N	W	K	2274290
69	C	E	V	D	S	Y	Q	T	D	Q	I	T	F	A	K	S	G	G	I	P	R	Y	I	G	V	-	-	-	-	-	GI 425474
119	L	F	W	Q	F	L	H	P	H	L	L	V	L	G	V	A	V	V	L	A	L	G	A	A	L	V	N	V	Q	I	2274290
94	-	-	-	-	L	I	L	P	D	C	V	Y	L	F	G	A	I	L	G	A	F	V	A	A	V	M	N	V	Y	I	GI 425474
149	P	L	L	G	Q	L	V	E	V	V	A	K	Y	T	R	D	H	V	G	S	F	M	T	E	S	Q	N	L	S	2274290	
120	P	L	Y	L	G	D	F	V	S	S	L	S	R	C	V	V	T	H	E	G	-	F	V	S	A	V	Y	V	P	T	GI 425474
179	T	H	L	L	I	L	Y	G	V	Q	G	L	L	T	F	G	Y	L	V	L	L	S	H	V	G	E	R	M	A	V	2274290
149	L	R	L	C	S	S	Y	L	L	Q	S	L	S	T	F	L	Y	I	G	L	L	G	S	V	G	E	R	M	A	R	GI 425474

FIGURE 2A

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209	D	M	R	R	A	L	F	S	S	L	L	R	Q	D	I	T	F	F	D	A	N	K	T	G	Q	L	V	S	R	L	2274290
179	R	M	R	I	Q	L	F	R	K	L	V	Y	Q	D	V	A	Y	F	D	V	H	S	S	G	K	L	V	E	I	I	GI 425474
239	T	T	D	V	Q	E	F	K	S	S	F	K	L	V	I	S	Q	G	L	R	S	C	T	Q	V	A	G	C	L	V	2274290
209	G	S	D	V	Q	N	F	K	S	S	F	K	Q	C	I	S	Q	G	L	R	N	G	I	Q	V	V	G	S	V	F	GI 425474
269	S	L	S	M	L	S	T	R	L	T	L	L	M	V	A	T	P	A	L	M	G	V	G	T	L	M	G	S	G	2274290	
239	A	L	L	S	I	S	P	T	L	T	A	A	L	I	G	C	L	P	C	V	F	L	I	G	S	L	M	G	T	E	GI 425474
299	L	R	K	L	S	R	Q	C	Q	E	Q	I	A	R	A	M	G	V	A	D	E	A	L	G	N	V	R	T	V	R	2274290
269	L	R	H	I	S	R	E	V	Q	S	Q	N	S	L	F	A	S	L	I	D	E	A	F	S	H	I	R	T	V	K	GI 425474
329	A	F	A	M	E	Q	R	E	E	R	Y	G	A	E	L	E	A	C	R	C	R	A	E	E	L	G	R	G	I	2274290	
299	S	L	A	M	E	D	F	L	I	N	K	I	N	Y	N	V	D	K	A	K	M	L	S	E	K	L	S	F	G	I	GI 425474
359	A	L	F	Q	G	L	S	N	I	A	F	N	C	M	V	L	G	T	L	F	I	G	G	S	L	V	A	G	Q	Q	2274290
329	G	S	F	Q	G	L	S	N	L	T	L	N	G	V	V	L	G	V	L	Y	V	G	G	H	L	M	S	R	G	E	GI 425474

FIGURE 2B

7/12

389	L	T	G	G	D	L	M	S	F	L	V	A	S	Q	T	V	Q	R	S	M	A	N	L	S	V	L	F	G	Q	V	2274290	
359	L	D	A	G	H	L	M	S	F	L	A	T	T	Q	T	L	Q	R	S	L	T	Q	L	S	L	L	Y	G	Q	V	GI 425474	
419	V	R	G	L	S	A	G	A	R	V	F	E	Y	M	A	L	N	P	-	-	-	-	C	I	P	L	S	G	G	C	-	2274290
389	V	R	G	Y	T	A	L	K	R	I	H	D	I	L	A	L	P	S	G	I	G	S	I	P	S	S	S	S	S	L	GI 425474	
445	C	V	P	K	E	Q	L	R	G	-	-	-	-	-	-	-	-	-	-	-	-	S	V	T	F	Q	N	V	C	2274290		
419	V	V	S	K	Q	H	V	N	N	I	K	E	L	P	S	S	S	I	Y	S	A	P	S	I	E	F	S	D	V	K	GI 425474	
462	F	S	Y	P	C	R	P	G	F	E	V	L	K	D	F	T	L	T	L	P	P	G	K	I	V	A	L	V	G	Q	2274290	
449	F	A	Y	P	N	R	P	E	T	I	V	L	N	E	L	S	M	F	L	P	G	K	V	I	A	L	V	G	Q	GI 425474		
492	S	G	G	G	K	T	T	V	A	S	L	L	E	R	F	Y	D	P	T	A	G	V	V	M	L	D	G	R	D	L	2274290	
479	S	G	A	G	K	S	T	V	V	S	L	L	E	R	F	Y	D	P	I	S	G	E	I	L	L	N	G	D	K	L	GI 425474	
522	R	T	L	D	P	S	W	L	R	G	Q	V	V	G	F	I	S	Q	E	P	V	L	F	G	T	I	M	E	N	2274290		
509	T	N	F	N	V	N	Y	L	R	S	K	L	I	G	Y	I	S	Q	E	P	Q	I	F	N	A	S	I	R	E	N	GI 425474	

FIGURE 2C

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552	I	R	F	G	K	L	E	A	S	D	E	E	V	Y	T	A	A	R	E	A	N	A	H	E	F	I	T	S	-	F	2274290
539	I	R	F	G	R	F	D	A	T	D	E	E	V	E	E	A	A	K	L	A	Y	A	H	D	F	I	S	N	D	L	GI 425474
581	P	E	G	Y	N	T	V	V	G	E	R	G	T	-	-	-	L	S	G	G	Q	K	Q	R	L	A	I	A	R	2274290	
569	P	Y	G	Y	D	T	L	V	G	Q	G	T	G	T	I	A	G	L	S	G	G	Q	R	Q	R	I	A	I	A	R	GI 425474
608	A	L	I	K	Q	P	T	V	L	I	L	D	E	A	T	S	A	L	D	A	E	S	E	R	V	V	Q	E	A	L	2274290
599	I	L	L	K	N	A	P	I	L	L	M	D	E	A	T	S	A	L	D	T	E	S	E	A	K	V	Q	N	A	L	GI 425474
638	D	R	A	S	A	G	R	T	V	L	V	I	A	H	R	L	S	T	V	R	G	A	H	C	I	V	V	M	A	D	2274290
629	N	N	A	M	K	G	R	T	V	L	I	I	A	H	R	L	S	T	V	R	K	A	D	L	I	L	V	M	S	K	GI 425474
668	G	R	V	W	E	A	G	T	H	E	E	L	L	K	K	G	G	L	Y	A	E	L	I	R	R	Q	A	L	D	A	2274290
659	G	Q	I	V	E	K	G	T	H	S	E	L	M	A	N	H	G	Y	Y	N	L	V	Q	R	Q	-	-	-	-	-	GI 425474
698	P	R	T	A	A	P	P	K	K	P	E	G	P	R	S	H	Q	H	K	S	2274290										
685	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	E	G	C	D	V	F	D	GI 425474							

FIGURE 2D

9/12

1	M	S	V	G	V	S	T	S	A	P	L	S	P	T	S	G	T	S	V	G	M	S	T	F	S	I	M	D	Y	V	2740029
1	M	T	V	A	-	S	T	A	A	P	S	Y	T	T	S	D	T	N	R	V	I	S	T	F	S	V	V	D	Y	V	GI 3015617
31	V	F	V	L	L	V	L	S	L	A	I	G	L	Y	H	A	C	R	G	W	G	R	H	T	V	G	E	L	L	2740029	
30	V	F	G	L	L	V	L	S	L	V	I	G	L	Y	H	A	C	R	G	W	G	R	H	T	V	G	E	L	L	GI 3015617	
61	M	A	D	R	K	M	G	C	L	P	V	A	L	S	L	L	A	T	F	Q	S	A	V	A	I	L	G	V	P	S	2740029
60	M	A	D	R	K	M	G	C	L	P	V	A	L	S	L	L	A	T	F	Q	S	A	V	A	I	L	G	P	A	GI 3015617	
91	E	I	Y	R	F	G	T	Q	Y	W	F	L	G	C	C	Y	F	L	G	L	L	I	P	A	H	I	F	I	P	V	2740029
90	E	I	Y	R	F	G	T	Q	Y	W	F	L	G	C	S	Y	F	L	G	L	L	I	P	A	H	I	F	I	P	V	GI 3015617
121	F	Y	R	L	H	L	T	S	A	Y	E	Y	L	E	L	R	F	N	K	T	V	R	V	C	G	T	V	T	F	I	2740029
120	F	Y	R	L	H	L	T	S	A	Y	E	Y	L	E	L	R	F	N	K	A	V	R	I	C	G	T	V	T	F	I	GI 3015617
151	F	Q	M	V	I	Y	M	G	V	V	L	Y	A	P	S	L	A	L	N	A	V	T	G	F	D	L	W	L	S	V	2740029
150	F	Q	M	V	V	Y	M	G	V	A	L	Y	A	P	S	L	A	L	N	A	V	T	G	F	D	L	W	L	S	V	GI 3015617

FIGURE 3A

10/12

181	L	A	L	G	I	V	C	T	V	Y	T	A	L	G	G	L	K	A	V	I	W	T	D	V	F	Q	T	L	V	M	2740029
180	L	A	L	G	I	V	C	N	I	Y	T	A	L	G	G	L	K	A	V	I	W	T	D	V	F	Q	T	L	I	M	GI 3015617
211	F	L	G	Q	L	A	V	I	I	V	G	S	A	K	V	G	G	L	G	R	V	W	A	V	A	S	Q	H	G	R	2740029
210	F	L	G	Q	L	V	V	I	I	V	G	A	A	K	V	G	G	L	G	H	V	W	A	V	A	S	Q	H	G	L	GI 3015617
241	I	S	G	F	E	L	D	P	D	P	F	V	R	H	T	F	W	T	L	A	F	G	G	V	F	M	M	L	S	L	2740029
240	I	S	G	I	E	L	D	P	D	P	F	V	R	H	T	F	W	T	L	A	F	G	G	V	F	M	M	L	S	L	GI 3015617
271	Y	G	V	N	Q	A	Q	V	Q	R	Y	L	S	S	R	T	E	K	A	A	V	L	S	C	Y	A	V	F	P	F	2740029
270	Y	G	V	N	Q	A	Q	V	Q	R	Y	L	S	S	H	S	E	K	A	A	V	L	S	C	Y	A	V	F	P	C	GI 3015617
301	Q	Q	V	S	L	C	V	G	C	L	I	G	L	V	M	F	A	Y	Y	Q	E	Y	P	M	S	I	Q	Q	A	Q	2740029
300	Q	Q	V	A	L	C	M	S	C	L	I	G	L	V	M	F	A	Y	Y	K	K	Y	S	M	S	P	Q	Q	E	Q	GI 3015617
331	A	A	P	D	Q	F	V	L	Y	F	V	M	D	L	L	K	G	L	P	G	L	P	G	L	F	I	A	C	L	F	2740029
330	A	A	P	D	Q	L	V	L	Y	F	V	M	D	L	L	K	D	M	P	G	L	P	G	L	F	V	A	C	L	F	GI 3015617

FIGURE 3B

11/12

361	S	G	S	L	S	T	I	S	S	A	F	N	S	L	A	T	V	T	M	E	D	L	I	R	P	W	F	P	E	F	2740029
360	S	G	S	L	S	T	I	S	S	A	F	N	S	L	A	T	V	T	M	E	D	L	I	Q	P	W	F	P	Q	L	GI 3015617
391	S	E	A	R	A	I	M	L	S	R	G	L	A	F	G	Y	G	L	L	C	L	G	M	A	Y	I	S	S	Q	M	2740029
390	T	E	T	R	A	I	M	L	S	R	S	L	A	F	A	Y	G	L	V	C	L	G	M	A	Y	V	S	S	H	L	GI 3015617
421	G	P	V	L	Q	A	A	I	S	I	F	G	M	V	G	G	P	L	L	G	L	F	C	L	G	M	F	F	P	C	2740029
420	G	S	V	L	Q	A	A	L	S	I	F	G	M	V	G	G	P	L	L	G	L	F	C	L	G	M	F	F	P	C	GI 3015617
451	A	N	P	P	G	A	V	V	G	L	L	A	G	L	V	M	A	F	W	I	G	I	G	S	I	V	T	S	M	G	2740029
450	A	N	P	L	G	A	I	V	G	L	L	T	G	L	T	M	A	F	W	I	G	I	G	S	I	V	S	R	M	S	GI 3015617
481	S	S	M	P	P	S	P	S	N	G	S	S	F	S	L	P	T	N	L	T	V	A	T	V	T	T	L	M	P	L	2740029
480	S	A	A	A	S	P	P	L	N	G	S	S	S	F	L	P	S	N	L	T	V	A	T	V	T	T	L	M	P	-	GI 3015617
511	T	T	F	S	K	P	T	G	L	Q	R	F	Y	S	L	S	Y	L	W	Y	S	A	H	N	S	T	T	V	I	V	2740029
509	S	T	L	S	K	P	T	G	L	Q	Q	F	Y	S	L	S	Y	L	W	Y	S	A	H	N	S	T	T	V	I	A	GI 3015617

FIGURE 3C

12/12

541	V	G	L	I	V	S	L	L	T	G	R	M	R	G	R	S	L	N	P	A	T	I	Y	P	V	L	P	K	L	L	2740029
539	V	G	L	I	V	S	L	L	T	G	R	M	R	G	R	S	L	N	P	G	T	I	Y	P	V	L	P	K	L	L	GI 3015617
571	S	L	L	P	L	S	C	Q	K	R	L	H	C	-	R	S	Y	G	Q	D	-	H	L	D	T	G	L	F	P	E	2740029
569	A	L	L	P	L	S	C	Q	K	R	L	-	C	W	R	S	H	N	Q	D	I	P	V	V	T	N	L	F	P	E	GI 3015617
599	K	P	R	N	G	V	L	G	D	S	R	D	K	E	A	M	A	L	D	G	T	A	Y	Q	G	S	S	S	T	C	2740029
598	K	M	G	N	G	A	L	Q	D	S	R	D	K	E	R	M	A	E	D	G	L	V	H	Q	P	C	S	P	T	Y	GI 3015617
629	I	L	Q	E	T	S	L	2740029																							
628	I	V	Q	E	T	S	L	GI 3015617																							

FIGURE 3D



## SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.  
 HILLMAN, Jennifer L.  
 YUE, Henry  
 TANG, Y. Tom  
 LAL, Preeti  
 CORLEY, Neil C.  
 GUEGLER, Karl J.  
 BAUGHN, Mariah R.  
 AZIMZAI, Yalda  
 LU, Dyung Aina M.

<120> MEMBRANE TRANSPORT PROTEINS

<130> PF-0633 PCT

<140> To Be Assigned

<141> Herewith

<150> 09/186,778; unassigned; 09/200,277; unassigned; 09/221,405;  
 unassigned; 60/121,896

<151> 1998-11-04; 1998-11-04; 1998-11-24; 1998-11-24; 1998-12-22;  
 1998-12-22; 1999-02-26

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1				5					10						
Ser	Ser	His	Leu	Val	Ser	Arg	Thr	Gln	Asp	Ile	His	Ile	Phe	Arg	
				20					25						30
Gln	Val	Thr	Ser	Arg	Gly	Glu	Ala	His	Leu	Glu	Leu	Asn	Ala	Phe	
				35					40						45
Arg	Arg	Lys	His	Asp	Cys	Ala	Leu	Val	Ile	Ser	Gly	Asp	Ser	Leu	
				50					55						60
Glu	Val	Cys	Leu	Lys	Tyr	Tyr	Glu	His	Glu	Phe	Val	Glu	Leu	Ala	
				65					70						75
Cys	Gln	Cys	Pro	Ala	Val	Val	Cys	Cys	Arg	Cys	Ser	Pro	Thr	Gln	
				80					85						90
Lys	Ala	Arg	Ile	Val	Thr	Leu	Leu	Gln	Gln	His	Thr	Gly	Arg	Arg	
				95					100						105

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Thr Cys Ala Ile Gly Asp Gly Gly Asn Asp Val Ser Met Ile Gln  
 110 115 120  
 Ala Ala Asp Cys Gly Ile Gly Ile Glu Gly Lys Glu Gly Lys Gln  
 125 130 135  
 Ala Ser Leu Ala Ala Asp Phe Ser Ile Thr Gln Phe Arg His Ile  
 140 145 150  
 Gly Arg Leu Leu Met Val His Gly Arg Asn Ser Tyr Lys Arg Ser  
 155 160 165  
 Ala Ala Leu Gly Gln Phe Val Met His Arg Gly Leu Ile Ile Ser  
 170 175 180  
 Thr Met Gln Ala Val Phe Ser Ser Val Phe Tyr Phe Ala Ser Val  
 185 190 195  
 Pro Leu Tyr Gln Gly Phe Leu Met Val Gly Tyr Ala Thr Ile Tyr  
 200 205 210  
 Thr Met Phe Pro Val Phe Ser Leu Val Leu Asp Gln Asp Val Lys  
 215 220 225  
 Pro Glu Met Ala Met Leu Tyr Pro Glu Leu Tyr Lys Asp Leu Thr  
 230 235 240  
 Lys Gly Arg Ser Leu Ser Phe Lys Thr Phe Leu Ile Trp Val Leu  
 245 250 255  
 Ile Ser Ile Tyr Gln Gly Gly Ile Leu Met Tyr Gly Ala Leu Val  
 260 265 270  
 Leu Phe Glu Ser Glu Phe Val His Val Val Ala Ile Ser Phe Thr  
 275 280 285  
 Ala Leu Ile Leu Thr Glu Leu Leu Met Val Ala Leu Thr Val Arg  
 290 295 300  
 Thr Trp His Trp Leu Met Val Val Ala Glu Phe Leu Ser Leu Gly  
 305 310 315  
 Cys Tyr Val Ser Ser Leu Ala Phe Leu Asn Glu Tyr Phe Gly Ile  
 320 325 330  
 Gly Arg Val Ser Phe Gly Ala Phe Leu Asp Val Ala Phe Ile Thr  
 335 340 345  
 Thr Val Thr Phe Leu Trp Lys Val Ser Ala Ile Thr Val Val Ser  
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 Cys Leu Pro Leu Tyr Val Leu Lys Tyr Leu Arg Arg Lys Leu Ser  
 365 370 375  
 Pro Pro Ser Tyr Cys Lys Leu Ala Ser  
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&lt;211&gt; 846

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3128782CD1

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 20 25 30  
 Gly Lys Lys Asp Lys Lys Ile Lys Lys Thr Phe Phe Glu Glu Leu

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Ala Val Glu Asp Lys Gln Ala Gly Glu Glu Glu Lys Val Leu Lys			
	50	55	60
Glu Lys Glu Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Lys			
	65	70	75
Lys Lys Arg Asp Thr Arg Lys Gly Arg Arg Lys Lys Asp Val Asp			
	80	85	90
Asp Asp Gly Glu Glu Lys Glu Leu Met Glu Arg Leu Lys Lys Leu			
	95	100	105
Ser Val Pro Thr Ser Asp Glu Glu Asp Glu Val Pro Ala Pro Lys			
	110	115	120
Pro Arg Gly Gly Lys Lys Thr Lys Gly Gly Asn Val Phe Ala Ala			
	125	130	135
Leu Ile Gln Asp Gln Ser Glu Glu Glu Glu Glu Glu Glu Lys His			
	140	145	150
Pro Pro Lys Pro Ala Lys Pro Glu Lys Asn Arg Ile Asn Lys Ala			
	155	160	165
Val Ser Glu Glu Gln Gln Pro Ala Leu Lys Gly Lys Lys Gly Lys			
	170	175	180
Glu Glu Lys Ser Lys Gly Lys Ala Lys Pro Gln Asn Lys Phe Ala			
	185	190	195
Ala Leu Asp Asn Glu Glu Glu Asp Lys Glu Glu Glu Ile Ile Lys			
	200	205	210
Glu Lys Glu Pro Pro Lys Gln Gly Lys Glu Lys Ala Lys Lys Ala			
	215	220	225
Glu Gln Gly Ser Glu Glu Glu Gly Glu Gly Glu Glu Glu Glu Glu			
	230	235	240
Glu Gly Gly Glu Ser Lys Ala Asp Asp Pro Tyr Ala His Leu Ser			
	245	250	255
Lys Lys Glu Lys Lys Lys Leu Lys Lys Gln Met Glu Tyr Glu Arg			
	260	265	270
Gln Val Ala Ser Leu Lys Ala Ala Asn Ala Ala Glu Asn Asp Phe			
	275	280	285
Ser Val Ser Gln Ala Glu Met Ser Ser Arg Gln Ala Met Leu Glu			
	290	295	300
Asn Ala Ser Asp Ile Lys Leu Glu Lys Phe Ser Ile Ser Ala His			
	305	310	315
Gly Lys Glu Leu Phe Val Asn Ala Asp Leu Tyr Ile Val Ala Gly			
	320	325	330
Arg Arg Tyr Gly Leu Val Gly Pro Asn Gly Lys Gly Lys Thr Thr			
	335	340	345
Leu Leu Lys His Ile Ala Asn Arg Ala Leu Ser Ile Pro Pro Asn			
	350	355	360
Ile Asp Val Leu Leu Cys Glu Gln Glu Val Val Ala Asp Glu Thr			
	365	370	375
Pro Ala Val Gln Ala Val Leu Arg Ala Asp Thr Lys Arg Leu Lys			
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Leu Leu Glu Glu Glu Arg Arg Leu Gln Gly Gln Leu Glu Gln Gly			
	395	400	405
Asp Asp Thr Ala Ala Glu Arg Leu Glu Lys Val Tyr Glu Glu Leu			
	410	415	420
Arg Ala Thr Gly Ala Ala Ala Ala Glu Ala Lys Ala Arg Arg Ile			
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Leu Ala Gly Leu Gly Phe Asp Pro Glu Met Gln Asn Arg Pro Thr			
	440	445	450

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Gln Lys Phe Ser Gly Gly Trp Arg Met Arg Val Ser Leu Ala Arg	455	460	465
Ala Leu Phe Met Glu Pro Thr Leu Leu Met Leu Asp Glu Pro Thr	470	475	480
Asn His Leu Asp Leu Asn Ala Val Ile Trp Leu Asn Asn Tyr Leu	485	490	495
Gln Gly Trp Arg Lys Thr Leu Leu Ile Val Ser His Asp Gln Gly	500	505	510
Phe Leu Asp Asp Val Cys Thr Asp Ile Ile His Leu Asp Ala Gln	515	520	525
Arg Leu His Tyr Tyr Arg Gly Asn Tyr Met Thr Phe Lys Lys Met	530	535	540
Tyr Gln Gln Lys Gln Lys Glu Leu Leu Lys Gln Tyr Glu Lys Gln	545	550	555
Glu Lys Lys Leu Lys Glu Leu Lys Ala Gly Gly Lys Ser Thr Lys	560	565	570
Gln Ala Glu Lys Gln Thr Lys Glu Ala Leu Thr Arg Lys Gln Gln	575	580	585
Lys Cys Arg Arg Lys Asn Gln Asp Glu Glu Ser Gln Glu Ala Pro	590	595	600
Glu Leu Leu Lys Arg Pro Lys Glu Tyr Thr Val Arg Phe Thr Phe	605	610	615
Pro Asp Pro Pro Pro Leu Ser Pro Pro Val Leu Gly Leu His Gly	620	625	630
Val Thr Phe Gly Tyr Gln Gly Gln Lys Pro Leu Phe Lys Asn Leu	635	640	645
Asp Phe Gly Ile Asp Met Asp Ser Arg Ile Cys Ile Val Gly Pro	650	655	660
Asn Gly Val Gly Lys Ser Thr Leu Leu Leu Leu Leu Thr Gly Lys	665	670	675
Leu Thr Pro Thr His Gly Glu Met Arg Lys Asn His Arg Leu Lys	680	685	690
Ile Gly Phe Phe Asn Gln Gln Tyr Ala Glu Gln Leu Arg Met Glu	695	700	705
Glu Thr Pro Thr Glu Tyr Leu Gln Arg Gly Phe Asn Leu Pro Tyr	710	715	720
Gln Asp Ala Arg Lys Cys Leu Gly Arg Phe Gly Leu Glu Ser His	725	730	735
Ala His Thr Ile Gln Ile Cys Lys Leu Ser Gly Gly Gln Lys Ala	740	745	750
Arg Val Val Phe Ala Glu Leu Ala Cys Arg Glu Pro Asp Val Leu	755	760	765
Ile Leu Asp Glu Pro Thr Asn Asn Leu Asp Ile Glu Ser Ile Asp	770	775	780
Ala Leu Gly Glu Ala Ile Asn Glu Tyr Lys Gly Ala Val Ile Val	785	790	795
Val Ser His Asp Ala Arg Leu Ile Thr Glu Thr Asn Cys Gln Leu	800	805	810
Trp Val Val Glu Glu Gln Ser Val Ser Gln Ile Asp Gly Asp Phe	815	820	825
Glu Asp Tyr Lys Arg Glu Val Leu Glu Ala Leu Gly Glu Val Met	830	835	840
Val Ser Arg Pro Arg Glu	845		

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 Asp Ala Leu Leu His Cys Leu Thr Thr Ser Arg Ala Arg Ala Leu  
 35 40 45  
 Val Phe Gly Ser Glu Met Ala Ser Ala Ile Cys Glu Val His Ala  
 50 55 60  
 Ser Leu Asp Pro Ser Leu Ser Leu Phe Cys Ser Gly Ser Trp Glu  
 65 70 75  
 Pro Gly Ala Val Pro Pro Ser Thr Glu His Leu Asp Pro Leu Leu  
 80 85 90  
 Lys Asp Ala Pro Lys His Leu Pro Ser Cys Pro Asp Lys Gly Phe  
 95 100 105  
 Thr Asp Lys Leu Phe Tyr Ile Tyr Thr Ser Gly Thr Thr Gly Leu  
 110 115 120  
 Pro Lys Ala Ala Ile Val Val His Ser Arg Tyr Tyr Arg Met Ala  
 125 130 135  
 Ala Leu Val Tyr Tyr Gly Phe Arg Met Arg Pro Asn Asp Ile Val  
 140 145 150  
 Tyr Asp Cys Leu Pro Leu Tyr His Ser Ala Gly Asn Ile Val Gly  
 155 160 165  
 Ile Gly Gln Cys Leu Leu His Gly Met Thr Val Val Ile Arg Lys  
 170 175 180  
 Lys Phe Ser Ala Ser Arg Phe Trp Asp Asp Cys Ile Lys Tyr Asn  
 185 190 195  
 Cys Thr Ile Val Gln Tyr Ile Gly Glu Leu Cys Arg Tyr Leu Leu  
 200 205 210  
 Asn Gln Pro Pro Arg Glu Ala Glu Asn Gln His Gln Val Arg Met  
 215 220 225  
 Ala Leu Gly Asn Gly Leu Arg Gln Ser Ile Trp Thr Asn Phe Ser  
 230 235 240  
 Ser Arg Phe His Ile Pro Gln Val Ala Glu Phe Tyr Gly Ala Thr  
 245 250 255  
 Glu Cys Asn Cys Ser Leu Gly Asn Phe Asp Ser Gln Val Gly Ala  
 260 265 270  
 Cys Gly Phe Asn Ser Arg Ile Leu Ser Ser Val Tyr Pro Ile Arg  
 275 280 285  
 Leu Val Arg Val Asn Glu Asp Thr Met Glu Leu Ile Arg Gly Pro  
 290 295 300  
 Asp Gly Val Cys Ile Pro Cys Gln Pro Gly Glu Pro Gly Gln Leu  
 305 310 315  
 Val Gly Arg Ile Ile Gln Lys Asp Pro Leu Arg Arg Phe Asp Gly  
 320 325 330  
 Tyr Leu Asn Gln Gly Ala Asn Asn Lys Lys Ile Ala Lys Asp Val

	335	340	345
Phe Lys Lys Gly Asp Gln Ala Tyr Leu Thr Gly Asp Val Leu Val			
	350	355	360
Met Asp Glu Leu Gly Tyr Leu Tyr Phe Arg Asp Arg Thr Gly Asp			
	365	370	375
Thr Phe Arg Trp Lys Gly Glu Asn Val Ser Thr Thr Glu Val Glu			
	380	385	390
Gly Thr Leu Ser Arg Leu Leu Asp Met Ala Asp Val Ala Val Tyr			
	395	400	405
Gly Val Glu Val Pro Gly Thr Glu Gly Arg Ala Gly Met Ala Ala			
	410	415	420
Val Ala Ser Pro Thr Gly Asn Cys Asp Leu Glu Arg Phe Ala Gln			
	425	430	435
Val Leu Glu Lys Glu Leu Pro Leu Tyr Ala Arg Pro Ile Phe Leu			
	440	445	450
Arg Leu Leu Pro Glu Leu His Lys Thr Gly Thr Tyr Lys Phe Gln			
	455	460	465
Lys Thr Glu Leu Arg Lys Glu Gly Phe Asp Pro Ala Ile Val Lys			
	470	475	480
Asp Pro Leu Phe Tyr Leu Asp Ala Gln Lys Gly Arg Tyr Val Pro			
	485	490	495
Leu Asp Gln Glu Ala Tyr Ser Arg Ile Gln Ala Gly Glu Glu Lys			
	500	505	510

Leu

&lt;210&gt; 4

&lt;211&gt; 718

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2274290CD1

&lt;400&gt; 4

Met Leu Val His Leu Phe Arg Val Gly Ile Arg Gly Gly Pro Phe		
1	5	10
Pro Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala		
	20	25
Val Arg Tyr Ser Asp Gly Tyr Arg Ser Ser Ser Leu Leu Arg Ala		
	35	40
Val Ala His Leu Arg Ser Gln Leu Trp Ala His Leu Pro Arg Ala		
	50	55
Pro Leu Ala Pro Arg Trp Ser Pro Ser Ala Trp Cys Trp Val Gly		
	65	70
Gly Ala Leu Leu Gly Pro Met Val Leu Ser Lys His Pro His Leu		
	80	85
Cys Leu Val Ala Leu Cys Glu Ala Glu Glu Ala Pro Pro Ala Ser		
	95	100
Ser Thr Pro His Val Val Gly Ser Arg Phe Asn Trp Lys Leu Phe		
	110	115
Trp Gln Phe Leu His Pro His Leu Leu Val Leu Gly Val Ala Val		
	125	130
Val Leu Ala Leu Gly Ala Ala Leu Val Asn Val Gln Ile Pro Leu		

WO 00/26245

	140	145	150
Leu Leu Gly Gln Leu Val Glu Val Val	Ala Lys Tyr Thr Arg Asp		
	155	160	165
His Val Gly Ser Phe Met Thr Glu Ser	Gln Asn Leu Ser Thr His		
	170	175	180
Leu Leu Ile Leu Tyr Gly Val Gln Gly	Leu Leu Thr Phe Gly Tyr		
	185	190	195
Leu Val Leu Leu Ser His Val Gly Glu	Arg Met Ala Val Asp Met		
	200	205	210
Arg Arg Ala Leu Phe Ser Ser Leu Leu	Arg Gln Asp Ile Thr Phe		
	215	220	225
Phe Asp Ala Asn Lys Thr Gly Gln Leu	Val Ser Arg Leu Thr Thr		
	230	235	240
Asp Val Gln Glu Phe Lys Ser Ser Phe	Lys Leu Val Ile Ser Gln		
	245	250	255
Gly Leu Arg Ser Cys Thr Gln Val Ala	Gly Cys Leu Val Ser Leu		
	260	265	270
Ser Met Leu Ser Thr Arg Leu Thr Leu	Leu Leu Met Val Ala Thr		
	275	280	285
Pro Ala Leu Met Gly Val Gly Thr Leu	Met Gly Ser Gly Leu Arg		
	290	295	300
Lys Leu Ser Arg Gln Cys Gln Glu Gln	Ile Ala Arg Ala Met Gly		
	305	310	315
Val Ala Asp Glu Ala Leu Gly Asn Val	Arg Thr Val Arg Ala Phe		
	320	325	330
Ala Met Glu Gln Arg Glu Glu Glu Arg	Tyr Gly Ala Glu Leu Glu		
	335	340	345
Ala Cys Arg Cys Arg Ala Glu Glu Leu	Gly Arg Gly Ile Ala Leu		
	350	355	360
Phe Gln Gly Leu Ser Asn Ile Ala Phe	Asn Cys Met Val Leu Gly		
	365	370	375
Thr Leu Phe Ile Gly Gly Ser Leu Val	Ala Gly Gln Gln Leu Thr		
	380	385	390
Gly Gly Asp Leu Met Ser Phe Leu Val	Ala Ser Gln Thr Val Gln		
	395	400	405
Arg Ser Met Ala Asn Leu Ser Val Leu	Phe Gly Gln Val Val Arg		
	410	415	420
Gly Leu Ser Ala Gly Ala Arg Val Phe	Glu Tyr Met Ala Leu Asn		
	425	430	435
Pro Cys Ile Pro Leu Ser Gly Gly Cys	Cys Val Pro Lys Glu Gln		
	440	445	450
Leu Arg Gly Ser Val Thr Phe Gln Asn	Val Cys Phe Ser Tyr Pro		
	455	460	465
Cys Arg Pro Gly Phe Glu Val Leu Lys	Asp Phe Thr Leu Thr Leu		
	470	475	480
Pro Pro Gly Lys Ile Val Ala Leu Val	Gly Gln Ser Gly Gly Gly		
	485	490	495
Lys Thr Thr Val Ala Ser Leu Leu Glu	Arg Phe Tyr Asp Pro Thr		
	500	505	510
Ala Gly Val Val Met Leu Asp Gly Arg	Asp Leu Arg Thr Leu Asp		
	515	520	525
Pro Ser Trp Leu Arg Gly Gln Val Val	Gly Phe Ile Ser Gln Glu		
	530	535	540
Pro Val Leu Phe Gly Thr Thr Ile Met	Glu Asn Ile Arg Phe Gly		
	545	550	555

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Lys Leu Glu Ala Ser Asp Glu Glu Val Tyr Thr Ala Ala Arg Glu  
 560 565 570  
 Ala Asn Ala His Glu Phe Ile Thr Ser Phe Pro Glu Gly Tyr Asn  
 575 580 585  
 Thr Val Val Gly Glu Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys  
 590 595 600  
 Gln Arg Leu Ala Ile Ala Arg Ala Leu Ile Lys Gln Pro Thr Val  
 605 610 615  
 Leu Ile Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu  
 620 625 630  
 Arg Val Val Gln Glu Ala Leu Asp Arg Ala Ser Ala Gly Arg Thr  
 635 640 645  
 Val Leu Val Ile Ala His Arg Leu Ser Thr Val Arg Gly Ala His  
 650 655 660  
 Cys Ile Val Val Met Ala Asp Gly Arg Val Trp Glu Ala Gly Thr  
 665 670 675  
 His Glu Glu Leu Leu Lys Lys Gly Gly Leu Tyr Ala Glu Leu Ile  
 680 685 690  
 Arg Arg Gln Ala Leu Asp Ala Pro Arg Thr Ala Ala Pro Pro Pro  
 695 700 705  
 Lys Lys Pro Glu Gly Pro Arg Ser His Gln His Lys Ser  
 710 715

&lt;210&gt; 5

&lt;211&gt; 635

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2740029CD1

&lt;400&gt; 5

Met Ser Val Gly Val Ser Thr Ser Ala Pro Leu Ser Pro Thr Ser  
 1 5 10 15  
 Gly Thr Ser Val Gly Met Ser Thr Phe Ser Ile Met Asp Tyr Val  
 20 25 30  
 Val Phe Val Leu Leu Val Leu Ser Leu Ala Ile Gly Leu Tyr  
 35 40 45  
 His Ala Cys Arg Gly Trp Gly Arg His Thr Val Gly Glu Leu Leu  
 50 55 60  
 Met Ala Asp Arg Lys Met Gly Cys Leu Pro Val Ala Leu Ser Leu  
 65 70 75  
 Leu Ala Thr Phe Gln Ser Ala Val Ala Ile Leu Gly Val Pro Ser  
 80 85 90  
 Glu Ile Tyr Arg Phe Gly Thr Gln Tyr Trp Phe Leu Gly Cys Cys  
 95 100 105  
 Tyr Phe Leu Gly Leu Leu Ile Pro Ala His Ile Phe Ile Pro Val  
 110 115 120  
 Phe Tyr Arg Leu His Leu Thr Ser Ala Tyr Glu Tyr Leu Glu Leu  
 125 130 135  
 Arg Phe Asn Lys Thr Val Arg Val Cys Gly Thr Val Thr Phe Ile  
 140 145 150  
 Phe Gln Met Val Ile Tyr Met Gly Val Val Leu Tyr Ala Pro Ser



	155	160	165
Leu Ala Leu Asn	Ala Val Thr Gly Phe	Asp Leu Trp Leu Ser	Val
	170	175	180
Leu Ala Leu Gly	Ile Val Cys Thr Val	Tyr Thr Ala Leu Gly	Gly
	185	190	195
Leu Lys Ala Val	Ile Trp Thr Asp Val	Phe Gln Thr Leu Val	Met
	200	205	210
Phe Leu Gly Gln	Leu Ala Val Ile Ile	Val Gly Ser Ala Lys	Val
	215	220	225
Gly Gly Leu Gly	Arg Val Trp Ala Val	Ala Ser Gln His Gly	Arg
	230	235	240
Ile Ser Gly Phe	Glu Leu Asp Pro Asp	Pro Phe Val Arg His	Thr
	245	250	255
Phe Trp Thr Leu	Ala Phe Gly Gly Val	Phe Met Met Leu Ser	Leu
	260	265	270
Tyr Gly Val Asn	Gln Ala Gln Val Gln	Arg Tyr Leu Ser Ser	Arg
	275	280	285
Thr Glu Lys Ala	Ala Val Leu Ser Cys	Tyr Ala Val Phe Pro	Phe
	290	295	300
Gln Gln Val Ser	Leu Cys Val Gly Cys	Leu Ile Gly Leu Val	Met
	305	310	315
Phe Ala Tyr Tyr	Gln Glu Tyr Pro Met	Ser Ile Gln Gln Ala	Gln
	320	325	330
Ala Ala Pro Asp	Gln Phe Val Leu Tyr	Phe Val Met Asp Leu	Leu
	335	340	345
Lys Gly Leu Pro	Gly Leu Pro Gly Leu	Phe Ile Ala Cys Leu	Phe
	350	355	360
Ser Gly Ser Leu	Ser Thr Ile Ser Ser	Ala Phe Asn Ser Leu	Ala
	365	370	375
Thr Val Thr Met	Glu Asp Leu Ile Arg	Pro Trp Phe Pro Glu	Phe
	380	385	390
Ser Glu Ala Arg	Ala Ile Met Leu Ser	Arg Gly Leu Ala Phe	Gly
	395	400	405
Tyr Gly Leu Leu	Cys Leu Gly Met Ala	Tyr Ile Ser Ser Gln	Met
	410	415	420
Gly Pro Val Leu	Gln Ala Ala Ile Ser	Ile Phe Gly Met Val	Gly
	425	430	435
Gly Pro Leu Leu	Gly Leu Phe Cys Leu	Gly Met Phe Phe Pro	Cys
	440	445	450
Ala Asn Pro Pro	Gly Ala Val Val Gly	Leu Leu Ala Gly Leu	Val
	455	460	465
Met Ala Phe Trp	Ile Gly Ile Gly Ser	Ile Val Thr Ser Met	Gly
	470	475	480
Ser Ser Met Pro	Pro Ser Pro Ser Asn	Gly Ser Ser Phe Ser	Leu
	485	490	495
Pro Thr Asn Leu	Thr Val Ala Thr Val	Thr Thr Leu Met Pro	Leu
	500	505	510
Thr Thr Phe Ser	Lys Pro Thr Gly Leu	Gln Arg Phe Tyr Ser	Leu
	515	520	525
Ser Tyr Leu Trp	Tyr Ser Ala His Asn	Ser Thr Thr Val Ile	Val
	530	535	540
Val Gly Leu Ile	Val Ser Leu Leu Thr	Gly Arg Met Arg Gly	Arg
	545	550	555
Ser Leu Asn Pro	Ala Thr Ile Tyr Pro	Val Leu Pro Lys Leu	Leu
	560	565	570

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<210> 6
<211> 535
<212> PRT
<213> Homo sapiens
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<220>  
<221> misc_feature  
<223> Incyte ID No: 2414415CD1
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<400> 6														
Met	Glu	Glu	Gly	Ala	Arg	His	Arg	Asn	Asn	Thr	Glu	Lys	Lys	His
1				5					10					15
Pro	Gly	Gly	Gly	Glu	Ser	Asp	Ala	Ser	Pro	Glu	Ala	Gly	Ser	Gly
				20					25					30
Gly	Gly	Gly	Val	Ala	Leu	Lys	Lys	Glu	Ile	Gly	Leu	Val	Ser	Ala
				35					40					45
Cys	Gly	Ile	Ile	Val	Gly	Asn	Ile	Ile	Gly	Ser	Gly	Ile	Phe	Val
				50					55					60
Ser	Pro	Lys	Gly	Val	Leu	Glu	Asn	Ala	Gly	Ser	Val	Gly	Leu	Ala
				65					70					75
Leu	Ile	Val	Trp	Ile	Val	Thr	Gly	Phe	Ile	Thr	Val	Val	Gly	Ala
				80					85					90
Leu	Cys	Tyr	Ala	Glu	Leu	Gly	Val	Thr	Ile	Pro	Lys	Ser	Gly	Gly
				95					100					105
Asp	Tyr	Ser	Tyr	Val	Lys	Asp	Ile	Phe	Gly	Gly	Leu	Ala	Gly	Phe
				110					115					120
Leu	Arg	Leu	Trp	Ile	Ala	Val	Leu	Val	Ile	Tyr	Pro	Thr	Asn	Gln
				125					130					135
Ala	Val	Ile	Ala	Leu	Thr	Phe	Ser	Asn	Tyr	Val	Leu	Gln	Pro	Leu
				140					145					150
Phe	Pro	Thr	Cys	Phe	Pro	Pro	Glu	Ser	Gly	Leu	Arg	Leu	Leu	Ala
				155					160					165
Ala	Ile	Cys	Leu	Leu	Leu	Leu	Thr	Trp	Val	Asn	Cys	Ser	Ser	Val
				170					175					180
Arg	Trp	Ala	Thr	Arg	Val	Gln	Asp	Ile	Phe	Thr	Ala	Gly	Lys	Leu
				185					190					195
Leu	Ala	Leu	Ala	Leu	Ile	Ile	Ile	Met	Gly	Ile	Val	Gln	Ile	Cys
				200					205					210
Lys	Gly	Glu	Tyr	Phe	Trp	Leu	Glu	Pro	Lys	Asn	Ala	Phe	Glu	Asn
				215					220					225
Phe	Gln	Glu	Pro	Asp	Ile	Gly	Leu	Val	Ala	Leu	Ala	Phe	Leu	Gln
				230					235					240
Gly	Ser	Phe	Ala	Tyr	Gly	Gly	Trp	Asn	Phe	Leu	Asn	Tyr	Val	Thr

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	245	250	255
Glu Glu Leu Val Asp	Pro Tyr Lys Asn	Leu Pro Arg Ala Ile	Phe
	260	265	270
Ile Ser Ile Pro	Leu Val Thr Phe Val	Tyr Val Phe Ala Asn	Val
	275	280	285
Ala Tyr Val Thr	Ala Met Ser Pro Gln	Glu Leu Leu Ala Ser	Asn
	290	295	300
Ala Val Ala Val	Thr Phe Gly Glu Lys	Leu Leu Gly Val Met	Ala
	305	310	315
Trp Ile Met Pro	Ile Ser Val Ala Leu	Ser Thr Phe Gly Gly	Val
	320	325	330
Asn Gly Ser Leu	Phe Thr Ser Ser Arg	Leu Phe Phe Ala Gly	Ala
	335	340	345
Arg Glu Gly His	Leu Pro Ser Val Leu	Ala Met Ile His Val	Lys
	350	355	360
Arg Cys Thr Pro	Ile Pro Ala Leu Leu	Phe Thr Cys Ile Ser	Thr
	365	370	375
Leu Leu Met Leu	Val Thr Ser Asp Met	Tyr Thr Leu Ile Asn	Tyr
	380	385	390
Val Gly Phe Ile	Asn Tyr Leu Phe Tyr	Gly Val Thr Val Ala	Gly
	395	400	405
Gln Ile Val Leu	Arg Trp Lys Lys Pro	Asp Ile Pro Arg Pro	Ile
	410	415	420
Lys Ile Asn Leu	Leu Phe Pro Ile Ile	Tyr Leu Leu Phe Trp	Ala
	425	430	435
Phe Leu Leu Val	Phe Ser Leu Trp Ser	Glu Pro Val Val Cys	Gly
	440	445	450
Ile Gly Leu Ala	Ile Met Leu Thr Gly	Val Pro Val Tyr Phe	Leu
	455	460	465
Gly Val Tyr Trp	Gln His Lys Pro Lys	Cys Phe Ser Asp Phe	Ile
	470	475	480
Glu Leu Leu Thr	Leu Val Ser Gln Lys	Met Cys Val Val Val	Tyr
	485	490	495
Pro Glu Val Glu	Arg Gly Ser Gly Thr	Glu Glu Ala Asn Glu	Asp
	500	505	510
Met Glu Glu Gln	Gln Gln Pro Met Tyr	Gln Pro Thr Pro Thr	Lys
	515	520	525
Asp Lys Asp Val	Ala Gly Gln Pro Gln	Pro	
	530	535	

&lt;210&gt; 7

&lt;211&gt; 456

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2466714CD1

&lt;400&gt; 7

Met Glu Ala Ser Trp Gly Ser Phe Asn Ala Glu Arg Gly Trp Tyr		
	10	15
1	5	
Val Ser Val Gln Gln Pro Glu Glu Ala Glu Ala Glu Glu Leu Ser		
	25	30
	20	

WO 00/26245

Pro Leu Leu Ser Asn Glu Leu His Arg Gln Arg Ser Pro Gly Val	35	40	45
Ser Phe Gly Leu Ser Val Phe Asn Leu Met Asn Ala Ile Met Gly	50	55	60
Ser Gly Ile Leu Gly Leu Ala Tyr Val Met Ala Asn Thr Gly Val	65	70	75
Phe Gly Phe Ser Phe Leu Leu Leu Thr Val Ala Leu Leu Ala Ser	80	85	90
Tyr Ser Val His Leu Leu Leu Ser Met Cys Ile Gln Thr Ala Val	95	100	105
Thr Ser Tyr Glu Asp Leu Gly Leu Phe Ala Phe Gly Leu Pro Gly	110	115	120
Lys Leu Val Val Ala Gly Thr Ile Ile Ile Gln Asn Ile Gly Ala	125	130	135
Met Ser Ser Tyr Leu Leu Ile Ile Lys Thr Glu Leu Pro Ala Ala	140	145	150
Ile Ala Glu Phe Leu Thr Gly Asp Tyr Asn Arg Tyr Trp Tyr Leu	155	160	165
Asp Gly Gln Thr Leu Leu Ile Ile Ile Cys Val Gly Ile Val Phe	170	175	180
Pro Leu Ala Leu Leu Pro Lys Ile Gly Phe Leu Gly Tyr Thr Ser	185	190	195
Ser Leu Ser Phe Phe Phe Met Met Phe Phe Ala Leu Val Val Ile	200	205	210
Ile Lys Lys Trp Ser Ile Pro Cys Pro Leu Thr Leu Asn Tyr Val	215	220	225
Glu Lys Gly Phe Gln Ile Ser Asn Val Thr Asp Asp Cys Lys Pro	230	235	240
Lys Leu Phe His Phe Ser Lys Glu Ser Ala Tyr Ala Leu Pro Thr	245	250	255
Met Ala Phe Ser Phe Leu Cys His Thr Ser Ile Leu Pro Ile Tyr	260	265	270
Cys Glu Leu Gln Ser Pro Ser Lys Lys Arg Met Gln Asn Val Thr	275	280	285
Asn Thr Ala Ile Ala Leu Ser Phe Leu Ile Tyr Phe Ile Ser Ala	290	295	300
Leu Phe Gly Tyr Leu Thr Phe Tyr Asp Lys Val Glu Ser Glu Leu	305	310	315
Leu Lys Gly Tyr Ser Lys Tyr Leu Ser His Asp Val Val Val Met	320	325	330
Thr Val Lys Leu Cys Ile Leu Phe Ala Val Leu Leu Thr Val Pro	335	340	345
Leu Ile His Phe Pro Ala Arg Lys Ala Val Thr Met Met Phe Phe	350	355	360
Ser Asn Phe Pro Phe Ser Trp Ile Arg His Phe Leu Ile Thr Leu	365	370	375
Ala Leu Asn Ile Ile Ile Val Leu Leu Ala Ile Tyr Val Pro Asp	380	385	390
Ile Arg Asn Val Phe Gly Val Val Gly Ala Ser Thr Ser Thr Cys	395	400	405
Leu Ile Phe Ile Phe Pro Gly Leu Phe Tyr Leu Lys Leu Ser Arg	410	415	420
Glu Asp Phe Leu Ser Trp Lys Lys Leu Gly Ala Phe Val Leu Leu	425	430	435
Ile Phe Gly Ile Leu Val Gly Asn Phe Ser Leu Ala Leu Ile Ile			

	440	445	450
Phe Asp Trp Ile Asn Lys			-
	455		

&lt;210&gt; 8

&lt;211&gt; 325

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2617942CD1

&lt;400&gt; 8

Met	Phe	Ala	Asn	Leu	Lys	Tyr	Val	Ser	Leu	Gly	Ile	Leu	Val	Phe
1				5					10					15
Gln	Thr	Thr	Ser	Leu	Val	Leu	Thr	Met	Arg	Tyr	Ser	Arg	Thr	Leu
				20					25					30
Lys	Glu	Glu	Gly	Pro	Arg	Tyr	Leu	Ser	Ser	Thr	Ala	Val	Val	Val
				35					40					45
Ala	Glu	Leu	Leu	Lys	Ile	Met	Ala	Cys	Ile	Leu	Leu	Val	Tyr	Lys
				50					55					60
Asp	Ser	Lys	Cys	Ser	Leu	Arg	Ala	Leu	Asn	Arg	Val	Leu	His	Asp
				65					70					75
Glu	Ile	Leu	Asn	Lys	Pro	Met	Glu	Thr	Leu	Lys	Leu	Ala	Ile	Pro
				80					85					90
Ser	Gly	Ile	Tyr	Thr	Leu	Gln	Asn	Asn	Leu	Leu	Tyr	Val	Ala	Leu
				95					100					105
Ser	Asn	Leu	Asp	Ala	Ala	Thr	Tyr	Gln	Val	Thr	Tyr	Gln	Leu	Lys
				110					115					120
Ile	Leu	Thr	Thr	Ala	Leu	Phe	Ser	Val	Ser	Met	Leu	Ser	Lys	Lys
				125					130					135
Leu	Gly	Val	Tyr	Gln	Trp	Leu	Ser	Leu	Val	Ile	Leu	Met	Thr	Gly
				140					145					150
Val	Ala	Phe	Val	Gln	Trp	Pro	Ser	Asp	Ser	Gln	Leu	Asp	Ser	Lys
				155					160					165
Glu	Leu	Ser	Ala	Gly	Ser	Gln	Phe	Val	Gly	Leu	Met	Ala	Val	Leu
				170					175					180
Thr	Ala	Cys	Phe	Ser	Ser	Gly	Phe	Ala	Gly	Val	Tyr	Phe	Glu	Lys
				185					190					195
Ile	Leu	Lys	Glu	Thr	Lys	Gln	Ser	Val	Trp	Ile	Arg	Asn	Ile	Gln
				200					205					210
Leu	Gly	Phe	Phe	Gly	Ser	Ile	Phe	Gly	Leu	Met	Gly	Val	Tyr	Ile
				215					220					225
Tyr	Asp	Gly	Glu	Leu	Val	Ser	Lys	Asn	Gly	Phe	Phe	Gln	Gly	Tyr
				230					235					240
Asn	Arg	Leu	Thr	Trp	Ile	Val	Val	Val	Leu	Gln	Ala	Leu	Gly	Gly
				245					250					255
Leu	Val	Ile	Ala	Ala	Val	Ile	Lys	Tyr	Ala	Asp	Asn	Ile	Leu	Lys
				260					265					270
Gly	Phe	Ala	Thr	Ser	Leu	Ser	Ile	Ile	Leu	Ser	Thr	Leu	Ile	Ser
				275					280					285
Tyr	Phe	Trp	Leu	Gln	Asp	Phe	Val	Pro	Thr	Ser	Val	Phe	Phe	Leu
				290					295					300

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<400> 10
Met Glu Arg Glu Met Glu Gly Arg Pro Leu His Asn Glu Gly Trp
  1                      5                      10                      15
Ile Asp Arg Ser Arg Val Gln Gln Lys Asp Leu Pro Asn Lys Cys

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	20	25	30
Pro Gln Thr Leu Trp Ser Glu Gln Ala Phe Pro Pro Asn Pro Gly			
	35	40	45
Gln Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu			
	50	55	60
Ala Ser Gly Leu Leu Arg Leu Pro Glu Ala Ala Glu Gly Gly Ile			
	65	70	75
Trp Ile Asp Gly Val Pro Ile Ala His Val Gly Leu His Thr Leu			
	80	85	90
Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile Leu Phe Pro			
	95	100	105
Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu His Ser Asp			
	110	115	120
Glu Ala Ile Trp Ala Ala Leu Glu Thr Val Gln Leu Lys Ala Leu			
	125	130	135
Val Ala Ser Leu Pro Gly Gln Leu Gln Tyr Lys Cys Ala Asp Arg			
	140	145	150
Gly Glu Asp Leu Ser Val Gly Gln Lys Gln Leu Leu Cys Leu Ala			
	155	160	165
Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile Leu Asp Glu Ala			
	170	175	180
Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met Gln Ala Met			
	185	190	195
Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu Ile Ala His			
	200	205	210
Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu Val Met Asp			
	215	220	225
Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln Leu Leu Ala			
	230	235	240
Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser Gly Leu Val			
	245	250	255

&lt;210&gt; 11

&lt;211&gt; 462

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1413743CD1

&lt;400&gt; 11

Met Ala Gln Val Ser Ile Asn Asn Asp Tyr Ser Glu Trp Asp Leu		
1	5	10
Ser Thr Asp Ala Gly Glu Arg Ala Arg Leu Leu Gln Ser Pro Cys		
	20	25
Val Asp Thr Ala Pro Lys Ser Glu Trp Glu Ala Ser Pro Gly Gly		
	35	40
Leu Asp Arg Gly Thr Thr Ser Thr Leu Gly Ala Ile Phe Ile Val		
	50	55
Val Asn Ala Cys Leu Gly Ala Gly Leu Leu Asn Phe Pro Ala Ala		
	65	70
Phe Ser Thr Ala Gly Gly Val Ala Ala Gly Ile Ala Leu Gln Met		
	80	85

Gly Met Leu Val Phe	Ile Ile Ser Gly	Leu Val Ile Leu Ala Tyr	95	100	105
Cys Ser Gln Ala Ser	Asn Glu Arg Thr	Tyr Gln Glu Val Val Trp	110	115	120
Ala Val Cys Gly Lys	Leu Thr Gly Val	Leu Cys Glu Val Ala Ile	125	130	135
Ala Val Tyr Thr Phe	Gly Thr Cys Ile	Ala Phe Leu Ile Ile Ile	140	145	150
Gly Asp Gln Gln Asp	Lys Ile Ile Ala	Val Met Ala Lys Glu Pro	155	160	165
Glu Gly Ala Ser Gly	Pro Trp Tyr Thr	Asp Arg Lys Phe Thr Ile	170	175	180
Ser Leu Thr Ala Phe	Leu Phe Ile Leu	Pro Leu Ser Ile Pro Arg	185	190	195
Glu Ile Gly Phe Gln	Lys Tyr Ala Ser	Phe Leu Ser Val Val Gly	200	205	210
Thr Trp Tyr Val Thr	Ala Ile Val Ile	Ile Lys Tyr Ile Trp Pro	215	220	225
Asp Lys Glu Met Thr	Pro Gly Asn Ile	Leu Thr Arg Pro Ala Ser	230	235	240
Trp Met Ala Val Phe	Asn Ala Met Pro	Thr Ile Cys Phe Gly Phe	245	250	255
Gln Cys His Val Ser	Ser Val Pro Val	Phe Asn Ser Met Gln Gln	260	265	270
Pro Glu Val Lys Thr	Trp Gly Gly Val	Val Thr Ala Ala Met Val	275	280	285
Ile Ala Leu Ala Val	Tyr Met Gly Thr	Gly Ile Cys Gly Phe Leu	290	295	300
Thr Phe Gly Ala Ala	Val Asp Pro Asp	Val Leu Leu Ser Tyr Pro	305	310	315
Ser Glu Asp Met Ala	Val Ala Val Ala	Arg Ala Phe Ile Ile Leu	320	325	330
Ser Val Leu Thr Ser	Tyr Pro Ile Leu	His Phe Cys Gly Arg Ala	335	340	345
Val Val Glu Gly Leu	Trp Leu Arg Tyr	Gln Gly Val Pro Val Glu	350	355	360
Glu Asp Val Gly Arg	Glu Arg Arg Arg	Arg Val Leu Gln Thr Leu	365	370	375
Val Trp Phe Leu Leu	Thr Leu Leu Leu	Ala Leu Phe Ile Pro Asp	380	385	390
Ile Gly Lys Val Ile	Ser Val Ile Gly	Gly Leu Ala Ala Cys Phe	395	400	405
Ile Phe Val Phe Pro	Gly Leu Cys Leu	Ile Gln Ala Lys Leu Ser	410	415	420
Glu Met Glu Glu Val	Lys Pro Ala Ser	Trp Trp Val Leu Val Ser	425	430	435
Tyr Gly Val Leu Leu	Val Thr Leu Gly	Ala Phe Ile Phe Gly Gln	440	445	450
Thr Thr Ala Asn Ala	Ile Phe Val Asp	Leu Leu Ala	455	460	

&lt;210&gt; 12

&lt;211&gt; 758

&lt;212&gt; PRT



&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1733477CD1

&lt;400&gt; 12

Met Gly Leu Ala Asp Ala Ser Gly Pro Arg Asp Thr Gln Ala Leu		
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Leu Ser Ala Thr Gln Ala Met Asp Leu Arg Arg Arg Asp Tyr His	20	25 30
Met Glu Arg Pro Leu Leu Asn Gln Glu His Leu Glu Glu Leu Gly	35	40 45
Arg Trp Gly Ser Ala Pro Arg Thr His Gln Trp Arg Thr Trp Leu	50	55 60
Gln Cys Ser Arg Ala Arg Ala Tyr Ala Leu Leu Gln His Leu	65	70 75
Pro Val Leu Val Trp Leu Pro Arg Tyr Pro Val Arg Asp Trp Leu	80	85 90
Leu Gly Asp Leu Leu Ser Gly Leu Ser Val Ala Ile Met Gln Leu	95	100 105
Pro Gln Gly Leu Ala Tyr Ala Leu Leu Ala Gly Leu Pro Pro Val	110	115 120
Phe Gly Leu Tyr Ser Ser Phe Tyr Pro Val Phe Ile Tyr Phe Leu	125	130 135
Phe Gly Thr Ser Arg His Ile Ser Val Gly Thr Phe Ala Val Met	140	145 150
Ser Val Met Val Gly Gly Val Thr Glu Ser Leu Ala Pro Gln Ala	155	160 165
Leu Asn Asp Ser Met Ile Asn Glu Thr Ala Arg Asp Ala Ala Arg	170	175 180
Val Gln Val Ala Ser Thr Leu Ser Val Leu Val Gly Leu Phe Gln	185	190 195
Val Gly Leu Gly Leu Ile His Phe Gly Phe Val Val Thr Tyr Leu	200	205 210
Ser Glu Pro Leu Val Arg Gly Tyr Thr Thr Ala Ala Ala Val Gln	215	220 225
Val Phe Val Ser Gln Leu Lys Tyr Val Phe Gly Leu His Leu Ser	230	235 240
Ser His Ser Gly Pro Leu Ser Leu Ile Tyr Thr Val Leu Glu Val	245	250 255
Cys Trp Lys Leu Pro Gln Ser Lys Val Gly Thr Val Val Thr Ala	260	265 270
Ala Val Ala Gly Val Val Leu Val Val Val Lys Leu Leu Asn Asp	275	280 285
Lys Leu Gln Gln Gln Leu Pro Met Pro Ile Pro Gly Glu Leu Leu	290	295 300
Thr Leu Ile Gly Ala Thr Gly Ile Ser Tyr Gly Met Gly Leu Lys	305	310 315
His Arg Phe Glu Val Asp Val Val Gly Asn Ile Pro Ala Gly Leu	320	325 330
Val Pro Pro Val Ala Pro Asn Thr Gln Leu Phe Ser Lys Leu Val	335	340 345
Gly Ser Ala Phe Thr Ile Ala Val Val Gly Phe Ala Ile Ala Ile	350	355 360

Ser Leu Gly Lys	Ile Phe Ala Leu Arg	His Gly Tyr Arg Val Asp	365	370	375
Ser Asn Gln Glu	Leu Val Ala Leu Gly	Leu Ser Asn Leu Ile Gly	380	385	390
Gly Ile Phe Gln	Cys Phe Pro Val Ser	Cys Ser Met Ser Arg Ser	395	400	405
Leu Val Gln Glu	Ser Thr Gly Gly Asn	Ser Gln Val Ala Gly Ala	410	415	420
Ile Ser Ser Leu	Phe Ile Leu Leu Ile	Ile Val Lys Leu Gly Glu	425	430	435
Leu Phe His Asp	Leu Pro Lys Ala Val	Leu Ala Ala Ile Ile Ile	440	445	450
Val Asn Leu Lys	Gly Met Leu Arg Gln	Leu Ser Asp Met Arg Ser	455	460	465
Leu Trp Lys Ala	Asn Arg Ala Asp Leu	Leu Ile Trp Leu Val Thr	470	475	480
Phe Thr Ala Thr	Ile Leu Leu Asn Leu	Asp Leu Gly Leu Val Val	485	490	495
Ala Val Ile Phe	Ser Leu Leu Leu Val	Val Val Arg Thr Gln Met	500	505	510
Pro His Tyr Ser	Val Leu Gly Gln Val	Pro Asp Thr Asp Ile Tyr	515	520	525
Arg Asp Val Ala	Glu Tyr Ser Glu Ala	Lys Glu Val Arg Gly Val	530	535	540
Lys Val Phe Arg	Ser Ser Ala Thr Val	Tyr Phe Ala Asn Ala Glu	545	550	555
Phe Tyr Ser Asp	Ala Leu Lys Gln Arg	Cys Gly Val Asp Val Asp	560	565	570
Phe Leu Ile Ser	Gln Lys Lys Lys Leu	Leu Lys Lys Gln Glu Gln	575	580	585
Leu Lys Leu Lys	Gln Leu Gln Lys Glu	Glu Lys Leu Arg Lys Gln	590	595	600
Ala Ala Ser Pro	Lys Gly Ala Ser Val	Ser Ile Asn Val Asn Thr	605	610	615
Ser Leu Glu Asp	Met Arg Ser Asn Asn	Val Glu Asp Cys Lys Met	620	625	630
Met Val Ser Ser	Gly Asp Lys Met Glu	Asp Ala Thr Ala Asn Gly	635	640	645
Gln Glu Asp Ser	Lys Ala Pro Asp Gly	Ser Thr Leu Lys Ala Leu	650	655	660
Gly Leu Pro Gln	Pro Asp Phe His Ser	Leu Ile Leu Asp Leu Gly	665	670	675
Ala Leu Ser Phe	Val Asp Thr Val Cys	Leu Lys Ser Leu Lys Asn	680	685	690
Ile Phe His Asp	Phe Arg Glu Ile Glu	Val Glu Val Tyr Met Ala	695	700	705
Ala Cys His Ser	Pro Val Val Ser Gln	Leu Glu Ala Gly His Phe	710	715	720
Phe Asp Ala Ser	Ile Thr Lys Lys His	Leu Phe Ala Ser Val His	725	730	735
Asp Ala Val Thr	Phe Ala Leu Gln His	Pro Arg Pro Val Pro Asp	740	745	750
Ser Pro Val Ser	Val Thr Arg Leu		755		

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<223> Incyte ID No: 2641908CD1
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335

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 <213> Homo sapiens

<220>  
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                                   20                                  25                                  30  
 Leu Ile Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg  
                                   35                                  40                                  45  
 Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Asp Lys  
                                   50                                  55                                  60  
 Pro Pro Lys Phe Ala Met Ser Arg Glu Gln Met Ser Gln Ser Cys  
                                   65                                  70                                  75  
 Ser His Thr Ala His Asn Ala Ser Leu Leu Thr Asp Ala Gly Pro  
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 Leu Ser Cys Gly Glu Ser Arg Ala Ser Cys Leu Phe Leu  
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 <213> Homo sapiens

<220>  
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                                   20                                  25                                  30  
 Ala Ser Ile Gly Leu Gln Thr Phe Asn His Ser Gly Ile Ser Val  
                                   35                                  40                                  45  
 Asn Ile Gln Asp Leu Ala Pro Ser Cys Ala Gly Phe Leu Phe Gly  
                                   50                                  55                                  60  
 Val Ala Asn Thr Ala Gly Ala Leu Ala Gly Val Val Gly Val Cys  
                                   65                                  70                                  75  
 Leu Gly Gly Tyr Leu Met Glu Thr Thr Gly Ser Trp Thr Cys Leu  
                                   80                                  85                                  90  
 Phe Asn Leu Val Ala Ile Ile Ser Asn Leu Gly Leu Cys Thr Phe  
                                   95                                  100                                  105  
 Leu Val Phe Gly Gln Ala Gln Arg Val Asp Leu Ser Ser Thr His  
                                   110                                  115                                  120

Glu Asp Leu

<210> 16  
 <211> 222  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 35 40 45  
 Asp Phe Ala Tyr Ser Asp Ser Arg Val Gly Phe Val Arg Gly Tyr  
 50 55 60  
 Ser Arg Arg Phe Trp Gln Gly Asp Thr Phe His Arg Gly Ser Asp  
 65 70 75  
 Lys Met Pro Gly Arg Val Val Thr Leu Leu Glu Asp His Glu Gly  
 80 85 90  
 Cys Thr Trp Gly Val Ala Tyr Gln Val Gln Gly Glu Gln Val Ser  
 95 100 105  
 Lys Ala Leu Lys Tyr Leu Asn Val Arg Glu Ala Val Leu Gly Gly  
 110 115 120  
 Tyr Asp Thr Lys Glu Val Thr Phe Tyr Pro Gln Asp Ala Pro Asp  
 125 130 135  
 Gln Pro Leu Lys Ala Leu Ala Tyr Val Ala Thr Pro Gln Asn Pro  
 140 145 150  
 Gly Tyr Leu Gly Pro Ala Pro Glu Glu Ala Ile Ala Thr Gln Ile  
 155 160 165  
 Leu Ala Cys Arg Gly Phe Ser Gly His Asn Leu Glu Tyr Leu Leu  
 170 175 180  
 Arg Leu Ala Asp Phe Met Gln Leu Cys Gly Pro Gln Ala Gln Asp  
 185 190 195  
 Glu His Leu Ala Ala Ile Val Asp Ala Val Gly Thr Met Leu Pro  
 200 205 210  
 Cys Phe Cys Pro Thr Glu Gln Ala Leu Ala Leu Val  
 215 220

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 <212> PRT  
 <213> Homo sapiens

<220>  
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20	25	30	
Met Thr Ala His	Ser Phe Ala Leu Pro Val	Ile Ile Phe Thr	Thr
35	40	45	
Phe Trp Gly Leu	Val Gly Ile Ala Gly Pro	Trp Phe Val Pro	Lys
50	55	60	
Gly Pro Asn Arg	Gly Val Ile Ile Thr Met	Leu Val Ala Thr	Ala
65	70	75	
Val Cys Cys Tyr	Leu Phe Trp Leu Ile Ala	Ile Leu Ala Gln	Leu
80	85	90	
Asn Pro Leu Phe	Gly Pro Gln Leu Lys Asn	Glu Thr Ile Trp	Tyr
95	100	105	
Val Arg Phe Leu	Trp Glu		
110			

&lt;210&gt; 18

&lt;211&gt; 1303

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 961344CB1

&lt;400&gt; 18

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&lt;210&gt; 19

&lt;211&gt; 3395

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3128782CB1

&lt;400&gt; 19

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&lt;210&gt; 20

&lt;211&gt; 2549

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1720440CB1

&lt;400&gt; 20

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&lt;210&gt; 21

&lt;211&gt; 2562

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2274290CB1

&lt;400&gt; 21

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&lt;223&gt; Incyte ID No: 2466714CB1

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&lt;211&gt; 2580

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1733477CB1

&lt;400&gt; 29

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&lt;210&gt; 30

&lt;211&gt; 1481

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2641908CB1

&lt;400&gt; 30

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&lt;210&gt; 31

&lt;211&gt; 667

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2656554CB1

&lt;400&gt; 31

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&lt;210&gt; 32

&lt;211&gt; 1635

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2719228CB1

&lt;400&gt; 32

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<210> 33

<211> 1447

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte ID No: 3657824CB1

<400> 33

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&lt;211&gt; 657

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5378485CB1

&lt;400&gt; 34

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&lt;210&gt; 35

&lt;211&gt; 646

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;300&gt;

&lt;308&gt; GenBank ID No: g2612939

&lt;400&gt; 35

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  20          25          30
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  35          40          45
Ile Val Cys Lys Thr Ala Arg Arg Asp Leu Phe Gly Leu Ser Val
  50          55          60
Leu Ile Arg Val Arg Leu Glu Leu Arg Arg His Arg Arg Ala Gly
  65          70          75
Asp Thr Ile Pro Cys Ile Phe Gln Ala Val Ala Arg Arg Gln Pro
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Glu	Ser	Ile	Leu	Pro	Asp	Thr	Gln	Leu	Leu	Asp	Pro	Met	Leu	Ala	215	220	225
Glu	Ala	Pro	Thr	Thr	Pro	Leu	Ala	Gln	Ala	Pro	Gly	Lys	Gly	Met	230	235	240
Asp	Asp	Arg	Leu	Phe	Tyr	Ile	Tyr	Thr	Ser	Gly	Thr	Thr	Gly	Leu	245	250	255
Pro	Lys	Ala	Ala	Ile	Val	Val	His	Ser	Arg	Tyr	Tyr	Arg	Ile	Ala	260	265	270
Ala	Phe	Gly	His	His	Ser	Tyr	Ser	Met	Arg	Ala	Ala	Asp	Val	Leu	275	280	285
Tyr	Asp	Cys	Leu	Pro	Leu	Tyr	His	Ser	Ala	Gly	Asn	Ile	Met	Gly	290	295	300
Val	Gly	Gln	Cys	Val	Ile	Tyr	Gly	Leu	Thr	Val	Val	Leu	Arg	Lys	305	310	315
Lys	Phe	Ser	Ala	Ser	Arg	Phe	Trp	Asp	Asp	Cys	Val	Lys	Tyr	Asn	320	325	330
Cys	Thr	Val	Val	Gln	Tyr	Ile	Gly	Glu	Ile	Cys	Arg	Tyr	Leu	Leu	335	340	345
Arg	Gln	Pro	Val	Arg	Asp	Val	Glu	Gln	Arg	His	Arg	Val	Arg	Leu	350	355	360
Ala	Val	Gly	Asn	Gly	Leu	Arg	Pro	Ala	Ile	Trp	Glu	Glu	Phe	Thr	365	370	375
Gln	Arg	Phe	Gly	Val	Pro	Gln	Ile	Gly	Glu	Phe	Tyr	Gly	Ala	Thr	380	385	390
Glu	Cys	Asn	Cys	Ser	Ile	Ala	Asn	Met	Asp	Gly	Lys	Val	Gly	Ser	395	400	405
Cys	Gly	Phe	Asn	Ser	Arg	Ile	Leu	Thr	His	Val	Tyr	Pro	Ile	Arg	410	415	420
Leu	Val	Lys	Val	Asn	Glu	Asp	Thr	Met	Glu	Pro	Leu	Arg	Asp	Ser	425	430	435
Glu	Gly	Leu	Cys	Ile	Pro	Cys	Gln	Pro	Gly	Glu	Pro	Gly	Leu	Leu	440	445	450
Val	Gly	Gln	Ile	Asn	Gln	Gln	Asp	Pro	Leu	Arg	Arg	Phe	Asp	Gly	455	460	465
Tyr	Val	Ser	Asp	Ser	Ala	Thr	Asn	Lys	Lys	Ile	Ala	His	Ser	Val	470	475	480
Phe	Arg	Lys	Gly	Asp	Ser	Ala	Tyr	Leu	Ser	Gly	Asp	Val	Leu	Val	485	490	495
Met	Asp	Glu	Leu	Gly	Tyr	Met	Tyr	Phe	Arg	Asp	Arg	Ser	Gly	Asp	500	505	510
Thr	Phe	Arg	Trp	Arg	Gly	Glu	Asn	Val	Ser	Thr	Thr	Glu	Val	Glu			

	515	520	525
Ala Val Leu Ser	Arg Leu Leu Gly Gln Thr Asp Val Ala Val Tyr		
	530	535	540
Gly Val Ala Val	Pro Gly Val Glu Gly Lys Ala Gly Met Ala Ala		
	545	550	555
Ile Ala Asp Pro	His Ser Gln Leu Asp Pro Asn Ser Met Tyr Gln		
	560	565	570
Glu Leu Gln Lys	Val Leu Ala Ser Tyr Ala Arg Pro Ile Phe Leu		
	575	580	585
Arg Leu Leu Pro	Gln Val Asp Thr Thr Gly Thr Phe Lys Ile Gln		
	590	595	600
Lys Thr Arg Leu	Gln Arg Glu Gly Phe Asp Pro Arg Gln Thr Ser		
	605	610	615
Asp Arg Leu Phe	Phe Leu Asp Leu Lys Gln Gly Arg Tyr Val Pro		
	620	625	630
Leu Asp Glu Arg	Val His Ala Arg Ile Cys Ala Gly Asp Phe Ser		
	635	640	645
Leu			

&lt;210&gt; 36

&lt;211&gt; 691

&lt;212&gt; PRT

&lt;213&gt; Schistosoma mansoni

&lt;300&gt;

&lt;308&gt; GenBank ID No: g425474

&lt;400&gt; 36

Met Phe Ser Ala Leu Cys Arg Arg Gly Phe Leu Thr Asn Lys Val	
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Ser Gln Phe Arg Ser Thr Tyr Lys Cys Asp His Tyr Asn Leu Lys	
	20 25 30
Thr His Ile Lys Pro Leu Lys Cys Ser Ser Leu Arg Leu Thr	
	35 40 45
Val Gly Thr Gly Leu Phe Ile Ala Leu His Ser Lys Ile Ser Pro	
	50 55 60
Glu Ser Arg Ile Gln Thr Val Gln Cys Glu Val Asp Ser Tyr Gln	
	65 70 75
Thr Asp Gln Ile Thr Phe Ala Lys Ser Gly Gly Ile Pro Arg Tyr	
	80 85 90
Ile Gly Val Leu Ile Leu Pro Asp Cys Val Tyr Leu Phe Gly Ala	
	95 100 105
Ile Leu Gly Ala Phe Val Ala Ala Val Met Asn Val Tyr Ile Pro	
	110 115 120
Leu Tyr Leu Gly Asp Phe Val Ser Ser Leu Ser Arg Cys Val Val	
	125 130 135
Thr His Glu Gly Phe Val Ser Ala Val Tyr Val Pro Thr Leu Arg	
	140 145 150
Leu Cys Ser Ser Tyr Leu Leu Gln Ser Leu Ser Thr Phe Leu Tyr	
	155 160 165
Ile Gly Leu Leu Gly Ser Val Gly Glu Arg Met Ala Arg Arg Met	
	170 175 180
Arg Ile Gln Leu Phe Arg Lys Leu Val Tyr Gln Asp Val Ala Tyr	
	185 190 195

Phe Asp Val His	Ser Ser Gly Lys Leu Val	Glu Ile Ile Gly Ser	200	205	210
Asp Val Gln Asn	Phe Lys Ser Ser Phe Lys	Gln Cys Ile Ser Gln	215	220	225
Gly Leu Arg Asn	Gly Ile Gln Val Val Gly	Ser Val Phe Ala Leu	230	235	240
Leu Ser Ile Ser	Pro Thr Leu Thr Ala Ala	Leu Ile Gly Cys Leu	245	250	255
Pro Cys Val Phe	Leu Ile Gly Ser Leu Met	Gly Thr Glu Leu Arg	260	265	270
His Ile Ser Arg	Glu Val Gln Ser Gln Asn	Ser Leu Phe Ala Ser	275	280	285
Leu Ile Asp Glu	Ala Phe Ser His Ile Arg	Thr Val Lys Ser Leu	290	295	300
Ala Met Glu Asp	Phe Leu Ile Asn Lys Ile	Asn Tyr Asn Val Asp	305	310	315
Lys Ala Lys Met	Leu Ser Glu Lys Leu Ser	Phe Gly Ile Gly Ser	320	325	330
Phe Gln Gly Leu	Ser Asn Leu Thr Leu Asn	Gly Val Val Leu Gly	335	340	345
Val Leu Tyr Val	Gly Gly His Leu Met Ser	Arg Gly Glu Leu Asp	350	355	360
Ala Gly His Leu	Met Ser Phe Leu Ala Thr	Thr Gln Thr Leu Gln	365	370	375
Arg Ser Leu Thr	Gln Leu Ser Leu Leu Tyr	Gly Gln Val Val Arg	380	385	390
Gly Tyr Thr Ala	Leu Lys Arg Ile His Asp	Ile Leu Ala Leu Pro	395	400	405
Ser Gly Ile Gly	Ser Ile Pro Ser Ser Ser	Ser Ser Ser Leu Val Val	410	415	420
Ser Lys Gln His	Val Asn Asn Ile Lys Glu	Leu Pro Ser Ser Ser	425	430	435
Ile Tyr Ser Ala	Pro Ser Ile Glu Phe Ser	Asp Val Lys Phe Ala	440	445	450
Tyr Pro Asn Arg	Pro Glu Thr Ile Val Leu	Asn Glu Leu Ser Met	455	460	465
Phe Leu Pro Gly	Gly Lys Val Ile Ala Leu	Val Gly Gln Ser Gly	470	475	480
Ala Gly Lys Ser	Thr Val Val Ser Leu Leu	Glu Arg Phe Tyr Asp	485	490	495
Pro Ile Ser Gly	Glu Ile Leu Leu Asn Gly	Asp Lys Leu Thr Asn	500	505	510
Phe Asn Val Asn	Tyr Leu Arg Ser Lys Leu	Ile Gly Tyr Ile Ser	515	520	525
Gln Glu Pro Gln	Ile Phe Asn Ala Ser Ile	Arg Glu Asn Ile Arg	530	535	540
Phe Gly Arg Phe	Asp Ala Thr Asp Glu Glu	Val Glu Glu Ala Ala	545	550	555
Lys Leu Ala Tyr	Ala His Asp Phe Ile Ser	Asn Asp Leu Pro Tyr	560	565	570
Gly Tyr Asp Thr	Leu Val Gly Gln Gly Thr	Gly Thr Ile Ala Gly	575	580	585
Leu Ser Gly Gly	Gln Arg Gln Arg Ile Ala	Ile Ala Arg Ile Leu	590	595	600
Leu Lys Asn Ala	Pro Ile Leu Leu Met Asp	Glu Ala Thr Ser Ala			

<400> 37														
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Thr	Asn	Arg	Val	Ile	Ser	Thr	Phe	Ser	Val	Val	Asp	Tyr	Val	Val
				20					25					30
Phe	Gly	Leu	Leu	Leu	Val	Leu	Ser	Leu	Val	Ile	Gly	Leu	Tyr	His
				35					40					45
Ala	Cys	Arg	Gly	Trp	Gly	Arg	His	Thr	Val	Gly	Glu	Leu	Leu	Met
				50					55					60
Ala	Asp	Arg	Lys	Met	Gly	Cys	Leu	Pro	Val	Ala	Leu	Ser	Leu	Leu
				65					70					75
Ala	Thr	Phe	Gln	Ser	Ala	Val	Ala	Ile	Leu	Gly	Gly	Pro	Ala	Glu
				80					85					90
Ile	Tyr	Arg	Phe	Gly	Thr	Gln	Tyr	Trp	Phe	Leu	Gly	Cys	Ser	Tyr
				95					100					105
Phe	Leu	Gly	Leu	Leu	Ile	Pro	Ala	His	Ile	Phe	Ile	Pro	Val	Phe
				110					115					120
Tyr	Arg	Leu	His	Leu	Thr	Ser	Ala	Tyr	Glu	Tyr	Leu	Glu	Leu	Arg
				125					130					135
Phe	Asn	Lys	Ala	Val	Arg	Ile	Cys	Gly	Thr	Val	Thr	Phe	Ile	Phe
				140					145					150
Gln	Met	Val	Val	Tyr	Met	Gly	Val	Ala	Leu	Tyr	Ala	Pro	Ser	Leu
				155					160					165
Ala	Leu	Asn	Ala	Val	Thr	Gly	Phe	Asp	Leu	Trp	Leu	Ser	Val	Leu
				170					175					180
Ala	Leu	Gly	Ile	Val	Cys	Asn	Ile	Tyr	Thr	Ala	Leu	Gly	Gly	Leu
				185					190					195
Lys	Ala	Val	Ile	Trp	Thr	Asp	Val	Phe	Gln	Thr	Leu	Ile	Met	Phe
				200					205					210
Leu	Gly	Gln	Leu	Val	Val	Ile	Ile	Val	Gly	Ala	Ala	Lys	Val	Gly
				215					220					225
Gly	Leu	Gly	His	Val	Trp	Ala	Val	Ala	Ser	Gln	His	Gly	Leu	Ile
				230					235					240

Ser Gly Ile Glu	Leu Asp Pro Asp Pro	Phe Val Arg His Thr	Phe
	245	250	255
Trp Thr Leu Ala	Phe Gly Gly Val Phe	Met Met Leu Ser Leu	Tyr
	260	265	270
Gly Val Asn Gln	Ala Gln Val Gln Arg	Tyr Leu Ser Ser His	Ser
	275	280	285
Glu Lys Ala Ala	Val Leu Ser Cys Tyr	Ala Val Phe Pro Cys	Gln
	290	295	300
Gln Val Ala Leu	Cys Met Ser Cys Leu	Ile Gly Leu Val Met	Phe
	305	310	315
Ala Tyr Tyr Lys	Lys Tyr Ser Met Ser	Pro Gln Gln Glu Gln	Ala
	320	325	330
Ala Pro Asp Gln	Leu Val Leu Tyr Phe	Val Met Asp Leu Leu	Lys
	335	340	345
Asp Met Pro Gly	Leu Pro Gly Leu Phe	Val Ala Cys Leu Phe	Ser
	350	355	360
Gly Ser Leu Ser	Thr Ile Ser Ser Ala	Phe Asn Ser Leu Ala	Thr
	365	370	375
Val Thr Met Glu	Asp Leu Ile Gln Pro	Trp Phe Pro Gln Leu	Thr
	380	385	390
Glu Thr Arg Ala	Ile Met Leu Ser Arg	Ser Leu Ala Phe Ala	Tyr
	395	400	405
Gly Leu Val Cys	Leu Gly Met Ala Tyr	Val Ser Ser His Leu	Gly
	410	415	420
Ser Val Leu Gln	Ala Ala Leu Ser Ile	Phe Gly Met Val Gly	Gly
	425	430	435
Pro Leu Leu Gly	Leu Phe Cys Leu Gly	Met Phe Phe Pro Cys	Ala
	440	445	450
Asn Pro Leu Gly	Ala Ile Val Gly Leu	Leu Thr Gly Leu Thr	Met
	455	460	465
Ala Phe Trp Ile	Gly Ile Gly Ser Ile	Val Ser Arg Met Ser	Ser
	470	475	480
Ala Ala Ala Ser	Pro Pro Leu Asn Gly	Ser Ser Ser Phe Leu	Pro
	485	490	495
Ser Asn Leu Thr	Val Ala Thr Val Thr	Thr Leu Met Pro Ser	Thr
	500	505	510
Leu Ser Lys Pro	Thr Gly Leu Gln Gln	Phe Tyr Ser Leu Ser	Tyr
	515	520	525
Leu Trp Tyr Ser	Ala His Asn Ser Thr	Thr Val Ile Ala Val	Gly
	530	535	540
Leu Ile Val Ser	Leu Leu Thr Gly Gly	Met Arg Gly Arg Ser	Leu
	545	550	555
Asn Pro Gly Thr	Ile Tyr Pro Val Leu	Pro Lys Leu Leu Ala	Leu
	560	565	570
Leu Pro Leu Ser	Cys Gln Lys Arg Leu	Cys Trp Arg Ser His	Asn
	575	580	585
Gln Asp Ile Pro	Val Val Thr Asn Leu	Phe Pro Glu Lys Met	Gly
	590	595	600
Asn Gly Ala Leu	Gln Asp Ser Arg Asp	Lys Glu Arg Met Ala	Glu
	605	610	615
Asp Gly Leu Val	His Gln Pro Cys Ser	Pro Thr Tyr Ile Val	Gln
	620	625	630
Glu Thr Ser Leu			



<210> 38  
 <211> 507  
 <212> PRT  
 <213> Homo sapiens

<300>

<308> GenBank ID No: g3639058

<400> 38

Met	Ala	Gly	Ala	Gly	Pro	Lys	Arg	Arg	Ala	Leu	Ala	Ala	Pro	Ala	1	5	10	15
Ala	Glu	Glu	Lys	Glu	Glu	Ala	Arg	Glu	Lys	Met	Leu	Ala	Ala	Lys	20	25	30	
Ser	Ala	Asp	Gly	Ser	Ala	Pro	Ala	Gly	Glu	Gly	Glu	Gly	Val	Thr	35	40	45	
Leu	Gln	Arg	Asn	Ile	Thr	Leu	Leu	Asn	Gly	Val	Ala	Ile	Ile	Val	50	55	60	
Gly	Thr	Ile	Ile	Gly	Ser	Gly	Ile	Phe	Val	Thr	Pro	Thr	Gly	Val	65	70	75	
Leu	Lys	Glu	Ala	Gly	Ser	Pro	Gly	Leu	Ala	Leu	Val	Val	Trp	Ala	80	85	90	
Ala	Cys	Gly	Val	Phe	Ser	Ile	Val	Gly	Ala	Leu	Cys	Tyr	Ala	Glu	95	100	105	
Leu	Gly	Thr	Thr	Ile	Ser	Lys	Ser	Gly	Gly	Asp	Tyr	Ala	Tyr	Met	110	115	120	
Leu	Glu	Val	Tyr	Gly	Ser	Leu	Pro	Ala	Phe	Leu	Lys	Leu	Trp	Ile	125	130	135	
Glu	Leu	Leu	Ile	Ile	Arg	Pro	Ser	Ser	Gln	Tyr	Ile	Val	Ala	Leu	140	145	150	
Val	Phe	Ala	Thr	Tyr	Leu	Leu	Lys	Pro	Leu	Phe	Pro	Thr	Cys	Pro	155	160	165	
Val	Pro	Glu	Glu	Ala	Ala	Lys	Leu	Val	Ala	Cys	Leu	Cys	Val	Leu	170	175	180	
Leu	Leu	Thr	Ala	Val	Asn	Cys	Tyr	Ser	Val	Lys	Ala	Ala	Thr	Arg	185	190	195	
Val	Gln	Asp	Ala	Phe	Ala	Ala	Ala	Lys	Leu	Leu	Ala	Leu	Ala	Leu	200	205	210	
Ile	Ile	Leu	Leu	Gly	Phe	Val	Gln	Ile	Gly	Lys	Gly	Asp	Val	Ser	215	220	225	
Asn	Leu	Asp	Pro	Lys	Phe	Ser	Phe	Glu	Gly	Thr	Lys	Leu	Asp	Val	230	235	240	
Gly	Asn	Ile	Val	Leu	Ala	Leu	Tyr	Ser	Gly	Leu	Phe	Ala	Tyr	Gly	245	250	255	
Gly	Trp	Asn	Tyr	Leu	Asn	Phe	Val	Thr	Glu	Glu	Met	Ile	Asn	Pro	260	265	270	
Tyr	Arg	Asn	Leu	Pro	Leu	Ala	Ile	Ile	Ile	Ser	Leu	Pro	Ile	Val	275	280	285	
Thr	Leu	Val	Tyr	Val	Leu	Thr	Asn	Leu	Ala	Tyr	Phe	Thr	Thr	Leu	290	295	300	
Ser	Thr	Glu	Gln	Met	Leu	Ser	Ser	Glu	Ala	Val	Ala	Val	Asp	Phe	305	310	315	
Gly	Asn	Tyr	His	Leu	Gly	Val	Met	Ser	Trp	Ile	Ile	Pro	Val	Phe	320	325	330	
Val	Gly	Leu	Ser	Cys	Phe	Gly	Ser	Val	Asn	Gly	Ser	Leu	Phe	Thr				

	335		340		345
Ser Ser Arg Leu	Phe Phe Val Gly Ser Arg Glu Gly His Leu	Pro			
	350		355		360
Ser Ile Leu Ser	Met Ile His Pro Gln Leu Leu Thr Pro Val	Pro			
	365		370		375
Ser Leu Val Phe	Thr Cys Val Met Thr Leu Leu Tyr Ala Phe	Ser			
	380		385		390
Lys Asp Ile Phe	Ser Val Ile Asn Phe Phe Ser Phe Phe Asn	Trp			
	395		400		405
Leu Cys Val Ala	Leu Ala Ile Ile Gly Met Ile Trp Leu Arg	His			
	410		415		420
Arg Lys Pro Glu	Leu Glu Arg Pro Ile Lys Val Asn Leu Ala	Leu			
	425		430		435
Pro Val Phe Phe	Ile Leu Ala Cys Leu Phe Leu Ile Ala Val	Ser			
	440		445		450
Phe Trp Lys Thr	Pro Val Glu Cys Gly Ile Gly Phe Thr Ile	Ile			
	455		460		465
Leu Ser Gly Leu	Pro Val Tyr Phe Phe Gly Val Trp Trp Lys	Asn			
	470		475		480
Lys Pro Lys Trp	Leu Leu Gln Gly Ile Phe Ser Thr Thr Val	Leu			
	485		490		495
Cys Gln Lys Leu	Met Gln Val Val Pro Gln Glu Thr				
	500		505		

&lt;210&gt; 39

&lt;211&gt; 504

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1840045

&lt;400&gt; 39

Met Glu Ala Pro	Leu Gln Thr Glu Met Val Glu Leu Val Pro	Asn
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Gly Lys His Ser	Glu Gly Leu Leu Pro Val Ile Thr Pro Met	Ala
	20	25 30
Gly Asn Gln Arg	Val Glu Asp Pro Ala Arg Ser Cys Met Glu	Gly
	35	40 45
Lys Ser Phe Leu	Gln Lys Ser Pro Ser Lys Glu Pro His Phe	Thr
	50	55 60
Asp Phe Glu Gly	Lys Thr Ser Phe Gly Met Ser Val Phe Asn	Leu
	65	70 75
Ser Asn Ala Ile	Met Gly Ser Gly Ile Leu Gly Leu Ala Tyr	Ala
	80	85 90
Met Ala Asn Thr	Gly Ile Ile Leu Phe Leu Phe Leu Leu Thr	Ala
	95	100 105
Val Ala Leu Leu	Ser Ser Tyr Ser Ile His Leu Leu Leu Lys	Ser
	110	115 120
Ser Gly Val Val	Gly Ile Arg Ala Tyr Glu Gln Leu Gly Tyr	Arg
	125	130 135
Ala Phe Gly Thr	Pro Gly Lys Leu Ala Ala Leu Ala Ile	Thr
	140	145 150

Leu	Gln	Asn	Ile	Gly	Ala	Met	Ser	Ser	Tyr	Leu	Tyr	Ile	Ile	Lys
				155					160					165
Ser	Glu	Leu	Pro	Leu	Val	Ile	Gln	Thr	Phe	Leu	Asn	Leu	Glu	Glu
				170					175					180
Lys	Thr	Ser	Asp	Trp	Tyr	Met	Asn	Gly	Asn	Tyr	Leu	Val	Ile	Leu
				185					190					195
Val	Ser	Val	Thr	Ile	Ile	Leu	Pro	Leu	Ala	Leu	Met	Arg	Gln	Leu
				200					205					210
Gly	Tyr	Leu	Gly	Tyr	Ser	Ser	Gly	Phe	Ser	Leu	Ser	Cys	Met	Val
				215					220					225
Phe	Phe	Leu	Ile	Ala	Val	Ile	Tyr	Lys	Lys	Phe	His	Val	Pro	Cys
				230					235					240
Pro	Leu	Pro	Pro	Asn	Phe	Asn	Asn	Thr	Thr	Gly	Asn	Phe	Ser	His
				245					250					255
Val	Glu	Ile	Val	Lys	Glu	Lys	Val	Gln	Leu	Gln	Val	Glu	Pro	Glu
				260					265					270
Ala	Ser	Ala	Phe	Cys	Thr	Pro	Ser	Tyr	Phe	Thr	Leu	Asn	Ser	Gln
				275					280					285
Thr	Ala	Tyr	Thr	Ile	Pro	Ile	Met	Ala	Phe	Ala	Phe	Val	Cys	His
				290					295					300
Pro	Glu	Val	Leu	Pro	Ile	Tyr	Thr	Glu	Leu	Lys	Asp	Pro	Ser	Lys
				305					310					315
Lys	Lys	Met	Gln	His	Ile	Ser	Asn	Leu	Ser	Ile	Ala	Val	Met	Tyr
				320					325					330
Ile	Met	Tyr	Phe	Leu	Ala	Ala	Leu	Phe	Gly	Tyr	Leu	Thr	Phe	Tyr
				335					340					345
Asn	Gly	Val	Glu	Ser	Glu	Leu	Leu	His	Thr	Tyr	Ser	Lys	Val	Asp
				350					355					360
Pro	Phe	Asp	Val	Leu	Ile	Leu	Cys	Val	Arg	Val	Ala	Val	Leu	Thr
				365					370					375
Ala	Val	Thr	Leu	Thr	Val	Pro	Ile	Val	Leu	Phe	Pro	Val	Arg	Arg
				380					385					390
Ala	Ile	Gln	Gln	Met	Leu	Phe	Pro	Asn	Gln	Glu	Phe	Ser	Trp	Leu
				395					400					405
Arg	His	Val	Leu	Ile	Ala	Val	Gly	Leu	Leu	Thr	Cys	Ile	Asn	Leu
				410					415					420
Leu	Val	Ile	Phe	Ala	Pro	Asn	Ile	Leu	Gly	Ile	Phe	Gly	Val	Ile
				425					430					435
Gly	Ala	Thr	Ser	Ala	Pro	Phe	Leu	Ile	Phe	Ile	Phe	Pro	Ala	Ile
				440					445					450
Phe	Tyr	Phe	Arg	Ile	Met	Pro	Thr	Glu	Lys	Glu	Pro	Ala	Arg	Ser
				455					460					465
Thr	Pro	Lys	Ile	Leu	Ala	Leu	Cys	Phe	Ala	Met	Leu	Gly	Phe	Leu
				470					475					480
Leu	Met	Thr	Met	Ser	Leu	Ser	Phe	Ile	Ile	Ile	Asp	Trp	Ala	Ser
				485					490					495
Gly	Thr	Ser	Arg	His	Gly	Gly	Asn	His						
				500										

&lt;210&gt; 40

&lt;211&gt; 393

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1526438

&lt;400&gt; 40

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Met Ala Ala Val Gly Ala Gly Gly Ser Thr Ala Ala Pro Gly Pro
 1                    5                10                15
Gly Ala Val Ser Ala Gly Ala Leu Glu Pro Gly Thr Ala Ser Ala
 20                25                30
Ala His Arg Arg Leu Lys Tyr Ile Ser Leu Ala Val Leu Val Val
 35                40                45
Gln Asn Ala Ser Leu Ile Leu Ser Ile Arg Tyr Ala Arg Thr Leu
 50                55                60
Pro Gly Asp Arg Phe Phe Ala Thr Thr Ala Val Val Met Ala Glu
 65                70                75
Val Leu Lys Gly Leu Thr Cys Leu Leu Leu Leu Phe Ala Gln Lys
 80                85                90
Arg Gly Asn Val Lys His Leu Val Leu Phe Leu His Glu Ala Val
 95                100               105
Leu Val Gln Tyr Val Asp Thr Leu Lys Leu Ala Val Pro Ser Leu
110               115               120
Ile Tyr Thr Leu Gln Asn Asn Leu Gln Tyr Val Ala Ile Ser Asn
125               130               135
Leu Pro Ala Ala Thr Phe Gln Val Thr Tyr Gln Leu Lys Ile Leu
140               145               150
Thr Thr Ala Leu Phe Ser Val Leu Met Leu Asn Arg Ser Leu Ser
155               160               165
Arg Leu Gln Trp Ala Ser Leu Leu Leu Leu Phe Thr Gly Val Ala
170               175               180
Ile Val Gln Ala Gln Gln Ala Gly Gly Gly Gly Pro Arg Pro Leu
185               190               195
Asp Gln Asn Pro Gly Ala Gly Leu Ala Ala Val Val Ala Ser Cys
200               205               210
Leu Ser Ser Gly Phe Ala Gly Val Tyr Phe Glu Lys Ile Leu Lys
215               220               225
Gly Ser Ser Gly Ser Val Trp Leu Arg Asn Leu Gln Leu Gly Leu
230               235               240
Phe Gly Thr Ala Leu Gly Leu Val Gly Leu Trp Trp Ala Glu Gly
245               250               255
Thr Ala Val Ala Thr Arg Gly Phe Phe Phe Gly Tyr Thr Pro Ala
260               265               270
Val Trp Gly Val Val Leu Asn Gln Ala Phe Gly Gly Leu Leu Val
275               280               285
Ala Val Val Val Lys Tyr Ala Asp Asn Ile Leu Lys Gly Phe Ala
290               295               300
Thr Ser Leu Ser Ile Val Leu Ser Thr Val Ala Ser Ile Arg Leu
305               310               315
Phe Gly Phe His Val Asp Pro Leu Phe Ala Leu Gly Ala Gly Leu
320               325               330
Val Ile Gly Ala Val Tyr Leu Tyr Ser Leu Pro Arg Gly Ala Ala
335               340               345
Lys Ala Ile Ala Ser Ala Ser Ala Ser Ala Ser Gly Pro Cys Val
350               355               360
His Gln Gln Pro Pro Gly Gln Pro Pro Pro Pro Gln Leu Ser Ser
365               370               375
His Arg Gly Asp Leu Ile Thr Glu Pro Phe Leu Pro Lys Ser Val

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Leu Val Lys 380 385 390

<210> 41  
 <211> 893  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank ID No: g3335175

<400> 41  
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 1 5 10 15  
 Pro Thr Leu Gln Gly Leu Ser Phe Thr Val Arg Pro Gly Glu Leu  
 20 25 30  
 Leu Ala Val Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu  
 35 40 45  
 Ser Ala Val Leu Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser  
 50 55 60  
 Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln Pro Trp Val Phe  
 65 70 75  
 Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys Lys Tyr Glu  
 80 85 90  
 Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu Lys Lys  
 95 100 105  
 Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly Asp  
 110 115 120  
 Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu  
 125 130 135  
 Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp  
 140 145 150  
 Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu  
 155 160 165  
 Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val  
 170 175 180  
 Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile  
 185 190 195  
 Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe  
 200 205 210  
 Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn  
 215 220 225  
 Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg  
 230 235 240  
 Asn Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser  
 245 250 255  
 Arg Pro Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu  
 260 265 270  
 Asn Val Pro Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys  
 275 280 285  
 Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His  
 290 295 300  
 Trp Ile Val Phe Ile Phe Leu Ile Leu Leu Asn Thr Ala Ala Gln

	305	310	315
Val Ala Tyr Val	Leu Gln Asp Trp Trp	Leu Ser Tyr Trp Ala	Asn
	320	325	330
Lys Gln Ser Met	Leu Asn Val Thr Val	Asn Gly Gly Gly Asn	Val
	335	340	345
Thr Glu Lys Leu	Asp Leu Asn Trp Tyr	Leu Gly Ile Tyr Ser	Gly
	350	355	360
Leu Thr Val Ala	Thr Val Leu Phe Gly	Ile Ala Arg Ser Leu	Leu
	365	370	375
Val Phe Tyr Val	Leu Val Asn Ser Ser	Gln Thr Leu His Asn	Lys
	380	385	390
Met Phe Glu Ser	Ile Leu Lys Ala Pro	Val Leu Phe Phe Asp	Arg
	395	400	405
Asn Pro Ile Gly	Arg Ile Leu Asn Arg	Phe Ser Lys Asp Ile	Gly
	410	415	420
His Leu Asp Asp	Leu Leu Pro Leu Thr	Phe Leu Asp Phe Ile	Gln
	425	430	435
Thr Leu Leu Gln	Val Val Gly Val Val	Ser Val Ala Val Ala	Val
	440	445	450
Ile Pro Trp Ile	Ala Ile Pro Leu Val	Pro Leu Gly Ile Ile	Phe
	455	460	465
Ile Phe Leu Arg	Arg Tyr Phe Leu Glu	Thr Ser Arg Asp Val	Lys
	470	475	480
Arg Leu Glu Ser	Thr Thr Arg Ser Pro	Val Phe Ser His Leu	Ser
	485	490	495
Ser Ser Leu Gln	Gly Leu Trp Thr Ile	Arg Ala Tyr Lys Ala	Glu
	500	505	510
Glu Arg Cys Gln	Glu Leu Phe Asp Ala	His Gln Asp Leu His	Ser
	515	520	525
Glu Ala Trp Phe	Leu Phe Leu Thr Thr	Ser Arg Trp Phe Ala	Val
	530	535	540
Arg Leu Asp Ala	Ile Cys Ala Met Phe	Val Ile Ile Val Ala	Phe
	545	550	555
Gly Ser Leu Ile	Leu Ala Lys Thr Leu	Asp Ala Gly Gln Val	Gly
	560	565	570
Leu Ala Leu Ser	Tyr Ala Leu Thr Leu	Met Gly Met Phe Gln	Trp
	575	580	585
Cys Val Arg Gln	Ser Ala Glu Val Glu	Asn Met Met Ile Ser	Val
	590	595	600
Glu Arg Val Ile	Glu Tyr Thr Asp Leu	Glu Lys Glu Ala Pro	Trp
	605	610	615
Glu Tyr Gln Lys	Arg Pro Pro Pro Ala	Trp Pro His Glu Gly	Val
	620	625	630
Ile Ile Phe Asp	Asn Val Asn Phe Met	Tyr Ser Pro Gly Gly	Pro
	635	640	645
Leu Val Leu Lys	His Leu Thr Ala Leu	Ile Lys Ser Gln Glu	Lys
	650	655	660
Val Gly Ile Val	Gly Arg Thr Gly Ala	Gly Lys Ser Ser Leu	Ile
	665	670	675
Ser Ala Leu Phe	Arg Leu Ser Glu Pro	Glu Gly Lys Ile Trp	Ile
	680	685	690
Asp Lys Ile Leu	Thr Thr Glu Ile Gly	Leu His Asp Leu Arg	Lys
	695	700	705
Lys Met Ser Ile	Ile Pro Gln Glu Pro	Val Leu Phe Thr Gly	Thr
	710	715	720

Met Arg Lys Asn Leu Asp Pro Phe Lys Glu His Thr Asp Glu Glu		
	725	730 735
Leu Trp Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu		
	740	745 750
Asp Leu Pro Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser		
	755	760 765
Asn Phe Ser Val Lys Gln Arg Gln Leu Val Cys Leu Ala Arg Ala		
	770	775 780
Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala		
	785	790 795
Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln Lys Lys Ile Arg		
	800	805 810
Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala His Arg Leu		
	815	820 825
Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp Ser Gly		
	830	835 840
Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn Lys		
	845	850 855
Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu		
	860	865 870
Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Val Ile Leu Gln Lys		
	875	880 885
Lys Leu Ser Thr Tyr Trp Ser His		
	890	

&lt;210&gt; 42

&lt;211&gt; 453

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1279457

&lt;400&gt; 42

Met Ala Leu Arg Gly Phe Cys Ser Arg Trp Leu Arg Pro Ala Leu		
1	5	10 15
Ala Ile Gly Leu Phe Ala Ser Met Ala Ala Val Leu Leu Gly Gly		
	20	25 30
Ala Arg Ala Ser Arg Leu Leu Phe Gln Arg Leu Leu Trp Asp Val		
	35	40 45
Val Arg Ser Pro Ile Ser Phe Phe Glu Arg Thr Pro Ile Gly His		
	50	55 60
Leu Leu Asn Arg Phe Ser Lys Glu Thr Asp Thr Val Asp Val Asp		
	65	70 75
Ile Pro Asp Lys Leu Arg Ser Leu Leu Met Tyr Ala Phe Gly Leu		
	80	85 90
Leu Glu Val Ser Leu Val Val Glu Trp Pro Thr Pro Leu Pro Leu		
	95	100 105
Trp Pro Ser Cys His Cys Phe Ser Ser Thr Leu Gly Phe Arg Trp		
	110	115 120
Leu Ala Ala Asn Val Glu Leu Leu Gly Asn Gly Leu Val Phe Ala		
	125	130 135
Ala Ala Thr Cys Ala Val Leu Ser Lys Ala His Leu Ser Ala Gly		
	140	145 150

Leu Val Gly Phe Ser Val Ser Ala Ala Leu Gln Val Thr Gln Thr	155	160	165
Leu Gln Trp Val Val Arg Asn Trp Thr Asp Leu Glu Asn Ser Ile	170	175	180
Val Ser Val Glu Arg Met Gln Asp Tyr Ala Trp Thr Pro Lys Glu	185	190	195
Ala Pro Trp Arg Leu Pro Thr Cys Ala Ala Gln Pro Pro Trp Pro	200	205	210
Gln Gly Gly Gln Ile Glu Phe Arg Asp Phe Gly Leu Arg Tyr Arg	215	220	225
Pro Glu Leu Pro Leu Ala Val Gln Gly Val Ser Phe Lys Ile His	230	235	240
Ala Gly Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys	245	250	255
Ser Ser Leu Ala Ser Gly Leu Leu Arg Leu Gln Glu Ala Ala Glu	260	265	270
Gly Gly Ile Trp Ile Asp Gly Val Pro Ile Ala His Val Gly Val	275	280	285
His Thr Leu Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile	290	295	300
Leu Phe Pro Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu	305	310	315
His Ser Asp Glu Ala Ile Trp Ala Ala Leu Glu Thr Val Gln Leu	320	325	330
Lys Ala Leu Val Ala Cys Leu Pro Gly Gln Leu Gln Tyr Lys Cys	335	340	345
Ala Asp Arg Gly Glu Asp Leu Ser Val Gly Gln Lys Gln Leu Leu	350	355	360
Cys Leu Ala Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile Leu	365	370	375
Asp Glu Ala Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met	380	385	390
Gln Ala Met Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu	395	400	405
Ile Ala His Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu	410	415	420
Val Met Asp Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln	425	430	435
Leu Leu Ala Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser	440	445	450
Gly Leu Val			



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
11 May 2000 (11.05.2000)

PCT

(10) International Publication Number  
**WO 00/26245 A3**

(51) International Patent Classification<sup>7</sup>: C12N 15/12,  
C07K 14/47, 16/18, A61K 38/17, C12Q 1/68, C12N 1/21

(21) International Application Number: PCT/US99/26048

(22) International Filing Date:  
4 November 1999 (04.11.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/172,255 4 November 1998 (04.11.1998) US  
60/172,252 24 November 1998 (24.11.1998) US  
60/172,214 22 December 1998 (22.12.1998) US  
60/121,896 26 February 1999 (26.02.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US 60/172,255 (CIP)  
Filed on 4 November 1998 (04.11.1998)  
US 60/172,252 (CIP)  
Filed on 24 November 1998 (24.11.1998)  
US 60/172,214 (CIP)  
Filed on 22 December 1998 (22.12.1998)  
US 60/121,896 (CIP)  
Filed on 26 February 1999 (26.02.1999)

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(81) Designated States (national): AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:  
19 April 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/26245 A3

(54) Title: HUMAN MEMBRANE TRANSPORT PROTEINS

(57) Abstract: The invention provides human membrane transport proteins (MTRP) and polynucleotides which identify and encode MTRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MTRP.

## INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/JJ 99/26048

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12N15/12 C07K14/47 C07K16/18 A61K38/17 C12Q1/68  
C12N1/21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07K C12N A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X    A	<p>DATABASE GENEMBL [Online] 20 February 1998 (1998-02-20) HALLECK M.S. ET AL: "Homo sapiens putative ATPase mRNA, partial cds." XP002132693 Accession No. U78978 -&amp; HALLECK, M.S. ET AL.: "Multiple members of a third subfamily of P-type ATPases identified by genomic sequences and ESTs." GENOME RESEARCH, vol. 8, no. 4, April 1998 (1998-04), pages 354-361, XP002132690 figure 2B page 357</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-16,19, 20

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

15 March 2000

Date of mailing of the international search report

20. JUNI. 2000

Name and mailing address of the ISA

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Authorized officer

ALCONADA RODRIG., A

## INTERNATIONAL SEARCH REPORT

 Interna Application No  
 PCT/US 99/26048

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
3	X DATABASE GENEMBL [Online] 27 May 1998 (1998-05-27) STANCHI, F.: "Homo sapiens mRNA for putative ATPase, partial" XP002132694 Accession AJ006268 ---	1-16, 19, 20
1	A ALLIKMETS R ET AL: "Characterization of the human ABC superfamily: isolation and mapping of 21 new genes using the expressed sequence tags database." HUMAN MOLECULAR GENETICS, (1996 OCT) 5 (10) 1649-55., XP002132691 figures 2,3; table 1 ---	
1	A MASTROBERARDINO L ET AL: "Amino-acid transport by heterodimers of 4F2hc/CD98 and members of a permease family." NATURE, (1998 SEP 17) 395 (6699) 288-91., XP002132692 the whole document ---	
1	A SARDET C ET AL: "Molecular cloning, primary structure, and expression of the human growth factor-activatable Na <sup>+</sup> /H <sup>+</sup> antiporter." CELL, (1989 JAN 27) 56 (2) 271-80., XP000876824 the whole document -----	
3		

# INTERNATIONAL SEARCH REPORT

Int. onal application No.  
PCT/US 99/26048

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 17,18  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-16,19-20 (partially)

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## 1. Claims: 1-16,19-20 (partially)

Human polypeptide comprising the amino acid sequence of SEQ ID NO:1 or any variant having at least 90% amino acid identity with said sequence, the polynucleotide sequence encoding said polypeptide (SEQ ID NO:18) and any variant having at least 90% identity with said polynucleotide sequence; a polynucleotide that hybridizes with said polynucleotide; methods for detection of the polynucleotide; expression vectors and hosts for the recombinant expression of said polypeptide; method for the production of said polypeptide; antibodies against said polypeptide, agonists, antagonists, pharmaceutical compositions containing said polypeptide and uses thereof for the treatment or prevention of a disorder.

## 2. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:2 and the polynucleotide sequence of SEQ ID NO:19.

## 3. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:3 and the polynucleotide sequence of SEQ ID NO:20.

## 4. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:4 and the polynucleotide sequence of SEQ ID NO:21.

## 5. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:5 and the polynucleotide sequence of SEQ ID NO:22.

## 6. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:6 and the polynucleotide sequence of SEQ ID NO:23.

## 7. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequences of SEQ ID NO:7 and 11 and the respective polynucleotide sequences of SEQ ID NO:24 and 28.

## 8. Claims: 1-16,19-20 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:8 and the polynucleotide sequence of SEQ ID NO:25.

9. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:9 and the polynucleotide sequence of SEQ ID NO:26.

10. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:10 and the polynucleotide sequence of SEQ ID NO:27.

11. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:12 and the polynucleotide sequence of SEQ ID NO:29.

12. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:13 and the polynucleotide sequence of SEQ ID NO:30.

13. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:14 and the polynucleotide sequence of SEQ ID NO:31.

14. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:15 and the polynucleotide sequence of SEQ ID NO:32.

15. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:16 and the polynucleotide sequence of SEQ ID NO:33.

16. Claims: 1-16,19-20 (partially)

As subject 1, but comprising the polypeptide sequence of SEQ ID NO:17 and the polynucleotide sequence of SEQ ID NO:34.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17,18

Present claims 17 and 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is not to be found, however, for any of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has not been carried out for those claims which do not appear to be supported and disclosed, namely those parts relating to the agonists and antagonists of the polypeptides of the invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.